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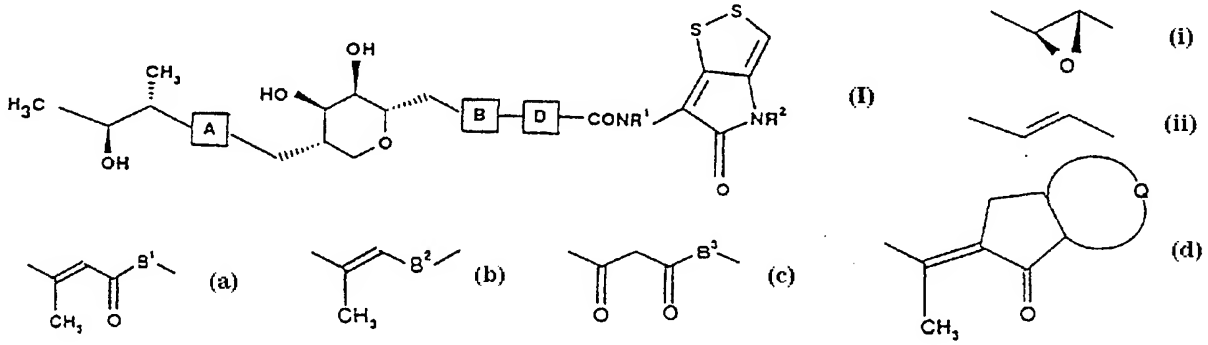

(57) Abstract

Derivatives of monic acids A and C of formula (I) in which: A is an epoxy moiety or an E-double bond moiety: (i) or (ii); B is selected from (a), (b), (c) (which corresponds to C(OH)=CHCO-B^3), (d) in which Q denotes the residue of an optionally substituted aryl or heteroaryl ring; D is a group of atoms for linking B with -$CONR^1$; or B-D represents (E)-$C(CH_3)$=CH; and R^1 and R^2, which may be the same or different, is each selected from hydrogen or (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, aryl, aryl(C_{1-4})alkyl, heterocyclyl, (C_{1-6})alkylcarbonyl, (C_{3-7})cycloalkylcarbonyl, (C_{2-6})alkenylcarbonyl, arylcarbonyl, aryl(C_{1-4})alkylcarbonyl or heterocyclylcarbonyl, each of which may be optionally substituted, have useful antibacterial, antimycoplasmal, antifungal and herbicidal activity.

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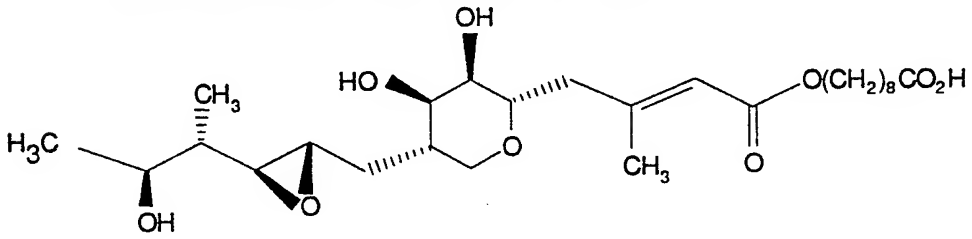
DERIVATIVES OF MONIC ACIDS A AND C HAVING ANTIBACTERIAL, ANTIMYCOPLASMATICAL, ANTIFUNGAL AND HERBICIDAL ACTIVITY

This invention relates to a novel class of compounds having antibacterial, antimycoplasmal and antifungal activity, to processes for their preparation and to their use in human and veterinary medicine, and also to intermediates for use in the preparation of such compounds. These compounds also have herbicidal activity and therefore will be of use in agriculture.

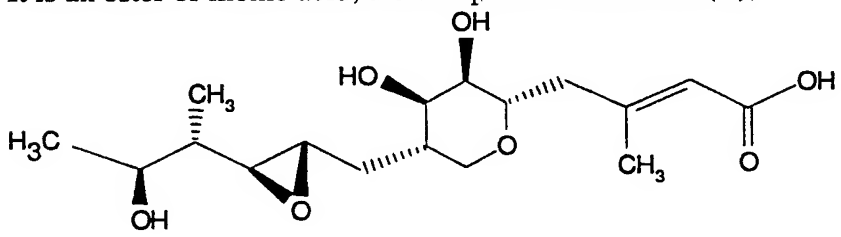
The microorganism *Pseudomonas fluorescens* produces three closely related tetrahydropyranyl compounds known as pseudomonic acids A, B and C which are of interest on account of their antibacterial properties.

Pseudomonic acid A (now known as mupirocin) has the structure (A):



(A)

It is an ester of monic acid, the compound of formula (B);

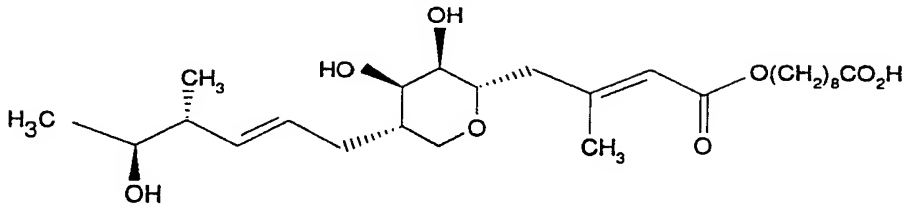


(B)

in which the ester forming radical is derived from 9-hydroxynonanoic acid.

Pseudomonic acid A exhibits good anti-bacterial activity, mainly against Gram-positive bacteria, but also against some Gram-negative bacteria such as *Haemophilus influenzae* and *Moraxella catarrhalis*. It acts as selective reversible inhibitor of bacterial *iso*-leucyl t-RNA synthetase, thereby inhibiting bacterial protein synthesis. It also has anti-mycoplasma and anti-fungal activity (see Merck Index, 11th edn, 1989, 993 and references therein and EP 0 251 434-A). The compound is marketed by Beecham Group plc under the trade mark Bactroban, as a topical formulation. Systematic use is precluded by a rapid metabolism to monic acid, which is inactive.

Pseudomonic acid C has the structure (C):



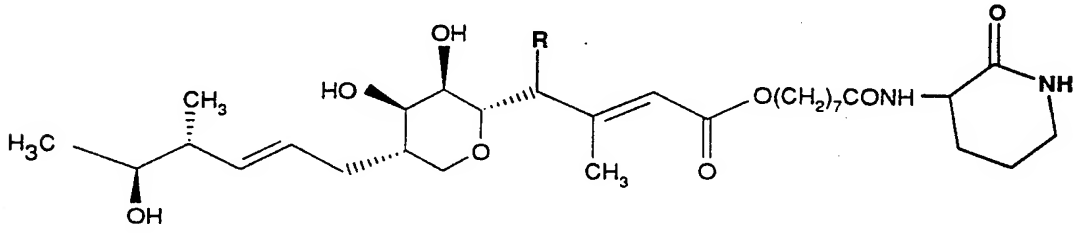
(C)

(EP 0 003 069, Beecham Group Ltd) and is distinguished from pseudomonic acid A by the presence of a C10-C11 *trans*-double bond.

The relative instability of pseudomonic acid A has limited the therapeutic use thereof to topical applications. Much effort has therefore been devoted to developing derivatives of pseudomonic acid A which retain the desirable antibacterial properties thereof but which are sufficiently stable to allow for systemic use. Attention has focussed on replacing the α,β-unsaturated ester moiety with a variety of other structural units which may be more resistant to enzymatic hydrolysis, for instance: α-methyl-α,β-unsaturated esters (EP 0 090 603-A); α,β-unsaturated thiol esters (EP 0 002 371-A); α,β-unsaturated amides (EP 0 001 914-A); α,β-unsaturated ketones (EP 0 029 665-A, WO 91/09855, WO 92/02518, J Med Chem, 1989, **32**, 151); β-hydroxy ketones (WO 93/06118), cyclic ketones (WO 94/02478) and 5- and 6-membered heterocyclic rings (EP 0 087 953-A, EP 0 123 378-A, EP 0 352 909-A, EP 0 399 645-A and WO 91/09856).

More recently, there have been reports of compounds produced by marine microrganisms which are closely related to pseudomonic acid and which have antibacterial activity. These compounds have the C10-C11 *trans*-double bond of the "C" series and, in certain instances, a hydroxyl substituent at C-4. In addition, the ester forming radical is derivable from 8-hydroxyoctanoic acid in which the carboxy terminal is present as an amide formed from an amine containing a heterocyclic moiety.

The compound of formula (D):

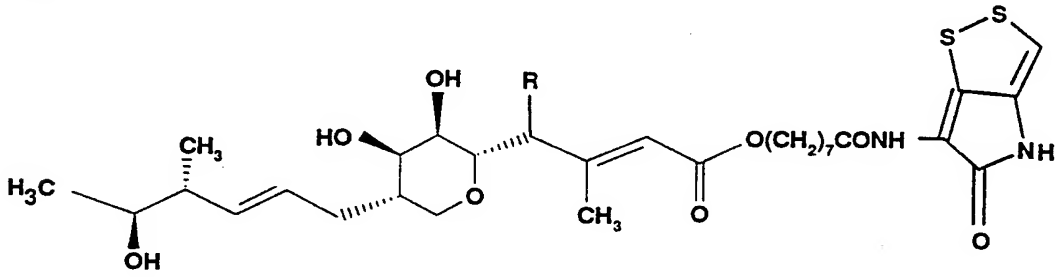


(D)

in which R is hydrogen or hydroxyl is produced by an *Alteromonas* species associated with a marine sponge (Stierle D B and Stierle A A, 200th National Meeting of ACS,

Washington DC, Aug 26-31, 1990 and Experientia, 1992, **48**, 1165). The stereochemistry of the C-4 hydroxyl was inferred to be β-, based on spectroscopic studies.

In addition, further compounds, named thiomarinol and thiomarinol C are produced by the microorganism *Alteromonas rava*. These have the general formula (E):

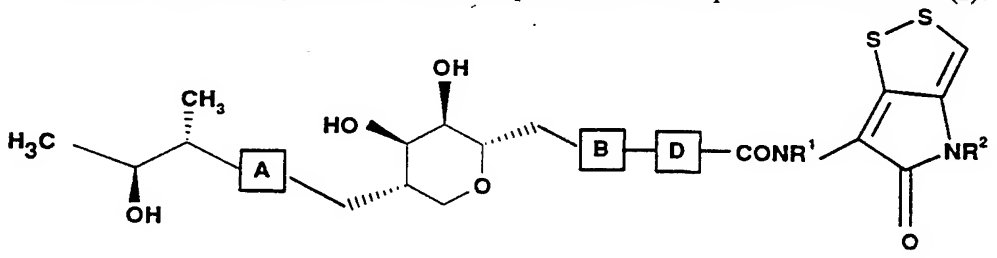


(E)

in which R is hydroxyl (thiomarinol) or hydrogen (thiomarinol C); the stereochemistry being the same as that in pseudomonic acid C at each of the common chiral centres. The stereochemistry of the 4-hydroxyl substituent, however, remains undefined [EP 0 512 824-A1, Sankyo Co Ltd and Shiozawa et al, J Antibiotics, 1993(12), 46, 1834-1842 (thiomarinol) and EP 0 595 458-A1, Sankyo Co Ltd (thiomarinol C)]. The thiomarinols are said to possess good anti-bacterial activity against both Gram-positive and Gram-negative organisms, as well as being active against mycoplasma. The amine forming the terminal amide is a pyrrothine, in particular a holothin. The acetamides thereof include the known anti-bacterial compounds thiolutin (Merck Index, 11th edn, 1989, 1471) and holomycin (Merck Index, 11th edn, 1989, 747). Thiolutin also has anti-fungal activity. It is expected that, for the thiomarinols, the presence of an α,β-unsaturated ester moiety will mean that the thiomarinols are susceptible to enzymatic hydrolysis.

We have now surprisingly found that derivatives of monic acid with improved anti-microbial properties may be obtained by incorporating a terminal 1,2-dithiolo[4,3-*b*]pyrrolone carbamoyl moiety.

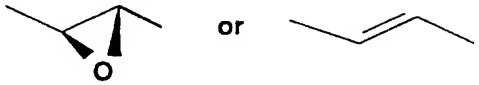
Accordingly, the present invention provides a compound of formula (I):



(I)

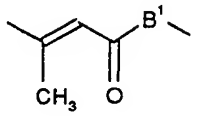
in which:

A is an epoxy moiety or an E-double bond moiety:



B is selected from the following:

(a)



in which:

B^1 is a group X^1, X^2, Y^1, NH or NHX^1,

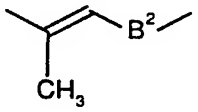
in which:

X^1 is optionally substitued aryl, preferably phenylene;

X^2 is (C_{1-10})alkylene, (C_{2-10})alkenylene, (C_{2-10})alkynylene, (C_{3-7})cycloalkylene or aryl(C_{1-4})alkylene, each of which may be optionally substituted; and

Y^1 is optionally substituted heterocyclyl, preferably heteroaryl;

(b)



in which:

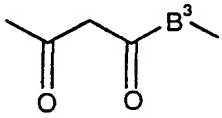
B^2 is Y^2, Y^2-X^1, Y^2-X^2 or Y^2-Y^3 in which:

Y^2 is a 5- or 6- membered heteroaryl ring having from 1 to 4 heteroatoms, preferably 1 to 3, most preferably 1 or 2, each selected from oxygen, sulphur or nitrogen and optionally substituted by (C_{1-10})alkyl, (C_{2-10})alkenyl, (C_{2-10})alkynyl, (C_{3-7})cycloalkyl, aryl(C_{1-4})alkyl, aryl or heterocyclyl;

Y^3 is an optionally substituted heterocyclic ring, preferably heteroaryl; and

X^1 and X^2 are as hereinbefore defined;

(c)

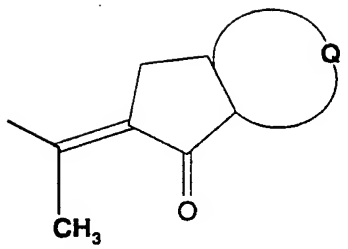


(which corresponds to C(OH)=CHCO-B^3),

in which B^3 is an optionally substituted hydrocarbyl or heterocyclyl group, suitably a group B^4-B^5 in which B^4 is (C_{1-6})alkylene, (C_{2-6})alkenylene, (C_{2-6})alkynylene and B^5 is a direct bond, (C_{3-7})cycloalkylene, (C_{4-7})cycloalkenylene, aryl or heteroaryl, each of which may be optionally substituted; or

B^4 is a bond and B^5 is (C_{3-7})cycloalkyene, (C_{4-7})cycloalkenylene, aryl or heteroaryl; or

(d)



in which Q denotes the residue of an optionally substituted aryl or heteroaryl ring;
D is a group of atoms for linking B with -CONR^1; or
B-D represents (E)-C(CH_3)=CH; and

R^1 and R^2, which may be the same or different, is each selected from hydrogen or (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, aryl, aryl(C_{1-4})alkyl, heterocyclyl, (C_{1-6})alkylcarbonyl, (C_{3-7})cycloalkylcarbonyl, (C_{2-6})alkenylcarbonyl, arylcarbonyl, aryl(C_{1-4})alkylcarbonyl or heterocyclylcarbonyl, each of which may be optionally substituted.

Compounds of formula (I) have improved anti-bacterial properties, in terms of absolute potency and/or an enhanced spectrum, compared to pseudomonic acids A and C.

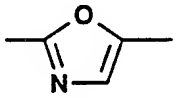
For convenience and by comparison with the convention used for the pseudomonic acids, compounds of formula (I) in which A is an epoxy moiety will be referred to as "A" series and compounds of formula (I) in which A is an E-double bond moiety will be referred to as "C" series.

The linking group of atoms D comprises one or more carbon atoms which may include carbon atoms in a carbocyclic, for instance, an aryl, ring and/or heteroatoms, for instance nitrogen, sulphur and oxygen, which could include heteroatoms in a heterocyclic ring.

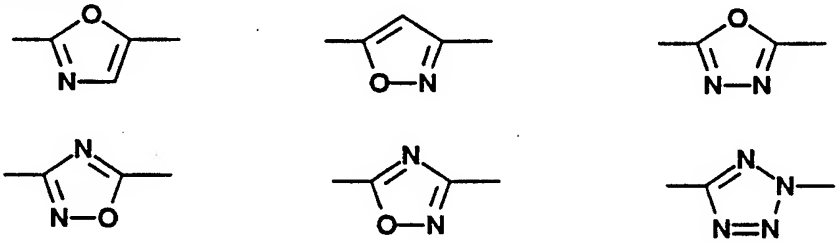
Suitably, D is a hydrocarbylene chain containing up to 20 carbon atoms, preferably a polymethylene chain having between between 1 and 20 carbon atoms, more preferably between 1 and 12 carbon atoms, which chain may be:
(a) optionally substituted, for instance by a (C_{1-6})alkyl group,
(b) optionally interrupted at one or more places by a moiety M,
(c) joined to B^1, B^2, B^3 or Q by a suitable linkage such as a direct bond, a heteroatom selected from oxygen, sulphur or nitrogen, carbonyloxy (COO), oxycarbonyl (OCO), carbonate(OCOO), carbamoyl (CONH), NHCO, NHCONH, SO_2 and SO_2NH, and
(d) joined to -CONR^1 by a suitable linkage such as a direct bond, optionally substituted (C_{3-7})cycloalkylene, optionally substitued aryl, preferably phenylene, or optionally substituted heterocyclyl, preferably heteroaryl; and
in which M represents a heteroatom selected from oxygen, sulphur or nitrogen,

preferably oxygen; a (C_{3-7})cycloalkylene group; a carbon-carbon double bond; a carbon-carbon triple bond; CO; OC(O); C(O)O; NRCO; C(O)NR; NRCONR; NRC(O)O; OC(O)NR; SO_2NR; $NRSO_2$; $CONRSO_2$; SO_2NRCO and phenyloxy; in which R is hydrogen or (C_{1-6})alkyl.

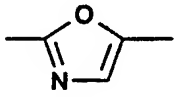
Suitable heteroaryl groups for Y^1 include: furan, thiophene, pyrrole, benzofuran, benzothiophene, indole, oxazole, isoxazole, thiazole, isothiazole, pyrazole, benzimidazole, oxadiazole, thiadiazole, triazole, tetrazole, thiatriazole, pyridine, quinoline, isoquinoline, pyrazine, pyrimidine, pyridazine and triazine; preferably thiophene, furan, pyrrole, thiazole, isothiazole, pyridine, pyrimidine, and quinoline. Preferably Y^1 is:



Suitable heteroaryl groups for Y^2 include furan, thiophene, pyrrole, diazole, oxazole, thiazole, isoxazole, isothiazole, triazole, oxadiazole, thiadiazole and tetrazole; preferably:



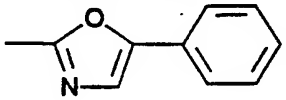
more preferably:



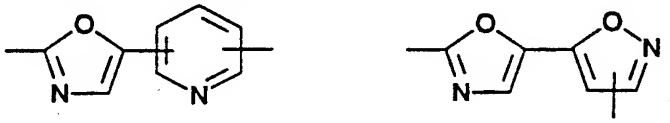
Suitable heteroaryl groups for Y^3 include:

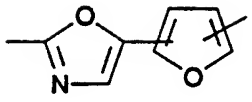
Suitable heteroaryl groups for B^5 include pyrimidine, thiazole, oxazole and pyridine. Suitable aryl groups for B^5 include phenylene.

Suitable combinations Y^2-X^1 include:



Suitable combinations Y^2-Y^3 include:

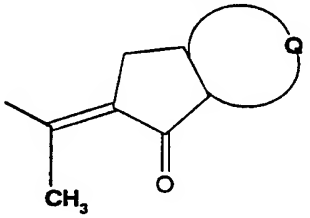




Suitably the aryl ring of which Q forms a residue is benzene or naphthalene, preferably benzene, which may be unsubstituted or substituted by up to three, suitably up to one further substituent, in addition to D.

Suitably the heteroaryl ring of which Q forms a residue includes both single and fused rings, with each ring suitably comprising up to four heteroatoms each selected from oxygen, nitrogen and sulphur, which rings may be unsubstituted or substituted by, for example, up to two further substituents, in addition to D. Each heteroaryl ring may have from 4 to 7, preferably 5 or 6, ring atoms. A fused heteroaryl ring may include an aryl ring and need include only one heteroaryl ring. Suitable fused heteroaryl rings include bicyclic systems. Preferably the heteroaryl ring of which Q forms a residue is a monocyclic heteroaryl ring, for instance pyridine or furan.

Representative examples of the moiety:



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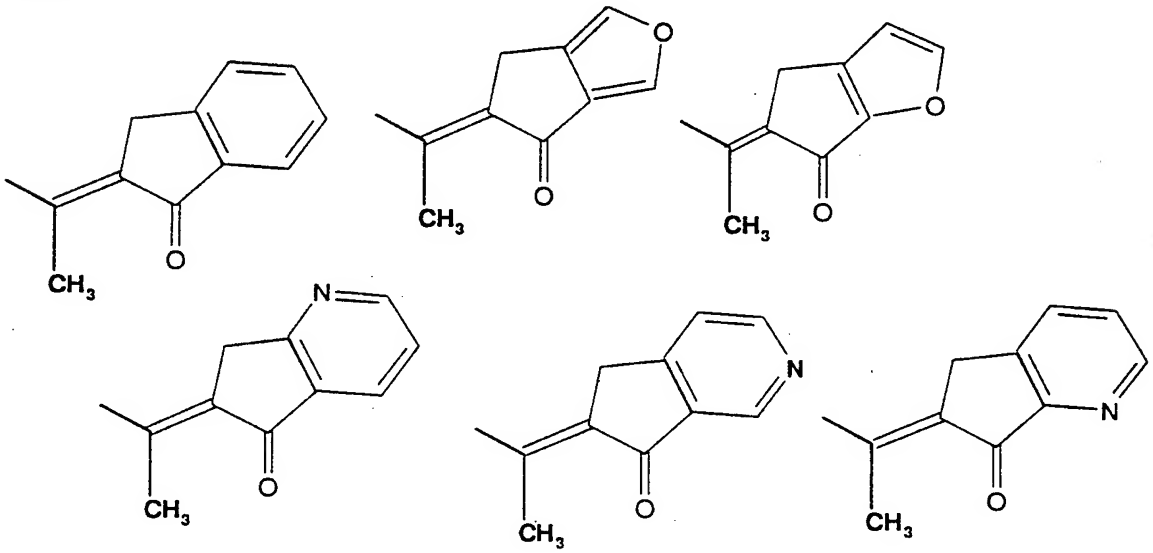
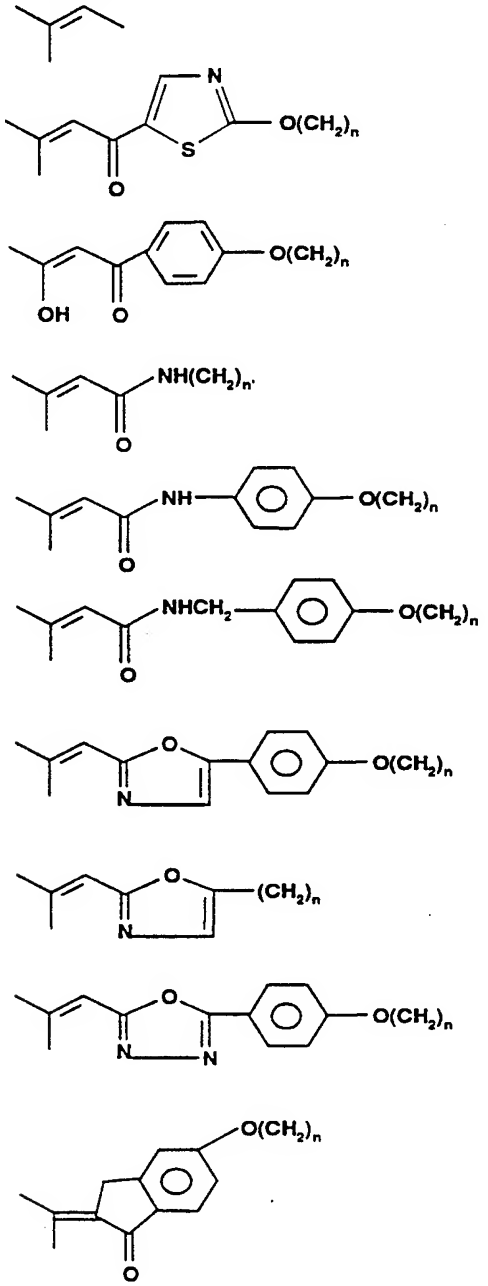


in each of which the aryl or heteroaryl ring may be optionally substituted. It will be appreciated that in these instances, the aryl ring of which Q forms a residue is

benzene and the heteroaryl ring of which Q forms a residue is furan or pyridine.

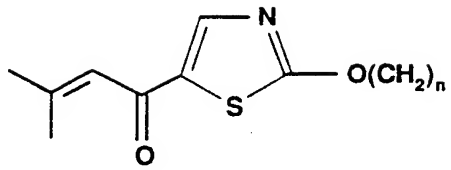
Suitably, D is an oxyalkylene chain $O(CH_2)_n$ or an alkylene chain $(CH_2)_n$ in which n is an integer between 1 and 12.

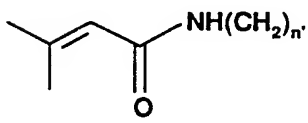
Suitable values for B-D include:

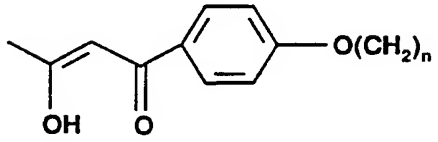


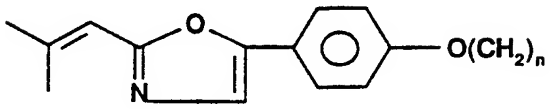
n = 1 to 6;
n'= 6 to 12

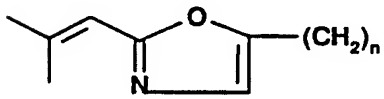
Preferred values for B-D include:

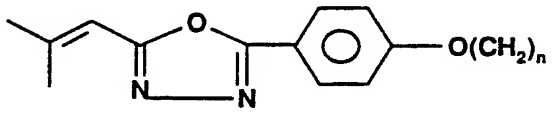


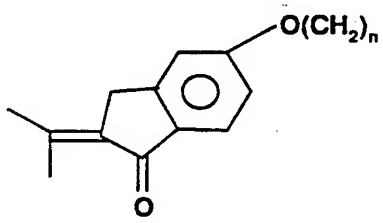












n = 1 to 6;
n'= 6 to 12

Suitably, R^1 is hydrogen or (C_{1-6})alkyl. Preferably R^1 is hydrogen.

Suitably, R^2 is hydrogen or (C_{1-6})alkyl, for instance methyl. Preferably R^2 is hydrogen.

Suitable substituents for a (C_{1-6})alkyl, (C_{3-7})cycloalkyl or (C_{2-6})alkenyl, group include for example, halogen, cyano, azido, nitro, carboxy, (C_{1-6})alkoxycarbonyl, carbamoyl, mono- or di-(C_{1-6})alkylcarbamoyl, sulpho,

sulphamoyl, mono- or di-(C_{1-6})alkylsulphamoyl, amino, mono- or di-(C_{1-6})alkylamino, acylamino, ureido, (C_{1-6})alkoxycarbonylamino, 2,2,2-trichloroethoxycarbonylamino, aryl, heterocyclyl, hydroxy, (C_{1-6})alkoxy, acyloxy, oxo, acyl, 2-thenoyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, hydroxyimino, (C_{1-6})alkoxyimino, hydrazino, hydrazono, benzohydroximoyl, guanidino, amidino and iminoalkylamino.

When used herein, the term 'halogen' refers to fluorine, chlorine, bromine or iodine.

When used herein, the term 'aryl' includes, unless otherwise defined, phenyl or naphthyl. When substituted, an aryl group may have up to five, preferably up to three substituents. Suitable such substituents include, for example, halogen, cyano, (C_{1-6})alkyl, phenyl, (C_{1-6})alkoxy, halo(C_{1-6})alkyl, hydroxy, amino, mono- or di-(C_{1-6})alkylamino, acylamino, nitro, carboxy, (C_{1-6})alkoxycarbonyl, (C_{1-6})-alkoxycarbonyl(C_{1-6})alkyl, (C_{1-6})alkylcarbonyloxy, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, sulphamoyl, mono- or di-(C_{1-6})alkylsulphamoyl, carbamoyl, and mono- or di-(C_{1-6})alkylcarbamoyl.

When used herein, the term 'heteroaryl' includes single and fused rings, each ring suitably comprising up to four, preferably 1 or 2, heteroatoms each selected from oxygen, nitrogen and sulphur. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A fused heteroaryl ring may include carbocyclic rings and need include only one heteroaryl ring. Suitable fused heteroaryl rings include bicyclic systems.

When used herein, the term 'heterocyclyl' includes aromatic and non-aromatic single or fused rings comprising up to four hetero-atoms in the ring selected from oxygen, nitrogen and sulphur and optionally substituted with up to three substituents. Suitably the heterocyclic ring comprises from 4 to 7, preferably 5 to 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need only include one heterocyclic ring.

When substituted, a heteroaryl or a heterocyclyl group may have up to three substituents. Suitable such substituents include those previously mentioned for an aryl group as well as oxo.

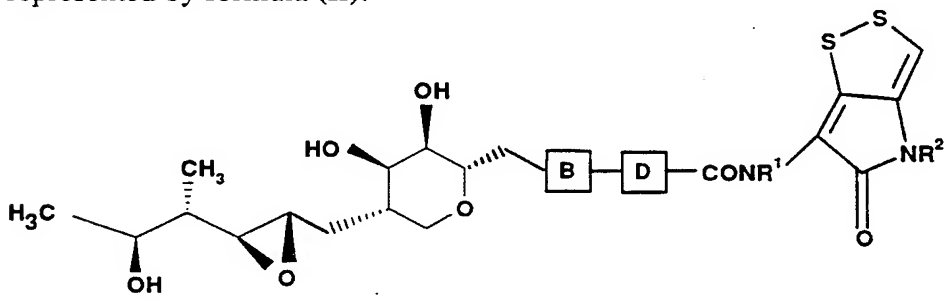
When used herein, the term 'hydrocarbylene' may include groups having up to 20 carbon atoms, suitably up to 10 carbon atoms, conveniently up to 6 carbon atoms. Suitable groups include (C_{1-6})alkylene, (C_{2-6})alkenylene, (C_{2-6})alkynylene, (C_{3-7})cycloalkylene, (C_{4-7})cycloalkenylene and aryl.

Since the compounds of formula (I) of the present invention are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations

of the compounds of formula (I) may be used for preparing the more pure forms used in the pharmaceutical compositions. Although the purity of intermediate compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Preferably, whenever possible, the compounds of the present invention are obtained in crystalline form.

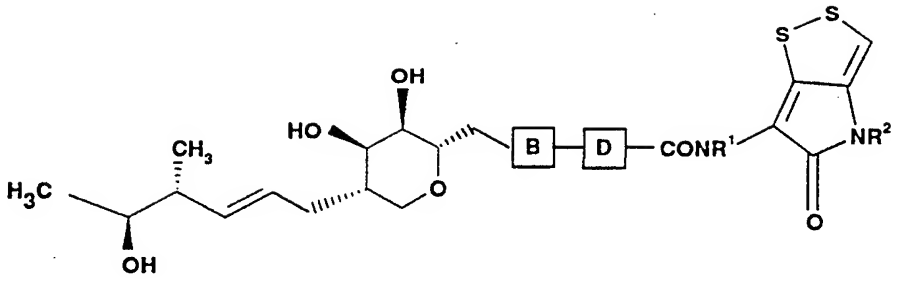
When some of the compounds of this invention are allowed to crystallise, or are recrystallised, from organic solvents. solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

It will be readily appreciated that compounds of formula (I) are derivatives of either monic acid A or monic acid C and as such have the same absolute configurations at corresponding chiral centres. Monic acid A is the name given to the compound 4-{(2S,3R,4R,5S)-5-[(2S,3S,4S,5S)-2,3-epoxy-5-hydroxy-4-methylhexyl]-3,4-dihydroxytetrahydropyran-2-yl}-3-methylbut-2(E)-enoic acid. Monic acid C is the name given to the compound 4-{(2S,3R,4R,5S)-5-[(4S,5S)-5-hydroxy-4-methylhex-2(E)-enyl]-3,4-dihydroxytetrahydropyran-2-yl}-3-methylbut-2(E)-enoic acid. Accordingly, within the compounds of formula (I), there exists a first sub-set of compounds which are derivatives of monic acid A and which may be represented by formula (II):



(II)

and a second sub-set of compounds which are derivatives of monic acid C and which may be represented by formula (III):



(III)

in which formulae B, D, R^1 and R^2 are as hereinbefore defined.

This invention also provides a pharmaceutical or veterinary composition which comprises a compound of formula (I) (hereinafter referred to as the 'drug') together with a pharmaceutically or veterinarily acceptable carrier or excipient. The compositions may be formulated for administration by any route, and would depend on the disease being treated. The compositions may be in the form of, for instance, tablets, capsules, powders, granules, suppositories, lozenges and liquid or gel preparations, including oral, topical and sterile parenteral suspensions.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics and cosmetics, such as Harry's Cosmeticology, 7th edn, ed Wilkinson and Moore, 1982, George Godwin, Harlow, England and the

British Pharmacopoeia.

Suppositories will contain conventional suppository bases, e.g. cocoa-butters or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the drug and a sterile vehicle. The drug, depending on the vehicle and concentration used, can be suspended in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability the composition can be frozen after filling into the vial and water removed under vacuum. The dry lypophilized powder is then sealed in the vial. The drug can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the drug.

For topical application to the ear, the drug may be made up into a suspension in a suitable liquid carrier, such as water, glycerol, diluted ethanol, propylene glycol, polyethylene glycol or fixed oils. For topical application to the eye, the drug is formulated as a suspension in a suitable, sterile aqueous or non-aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite or disodium edetate; preservatives including bactericidal and fungicidal agents, such as phenylmercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hypromellose may also be included.

The dosage employed for compositions administered topically will, of course, depend on the size of the area being treated. For the ears and eyes each dose will typically be in the range from 10 to 100 mg of the drug.

Veterinary compositions for intramammary treatment of mammary disorders in animals, especially bovine mastitis, will generally contain a suspension of the drug in an oily vehicle.

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the drug, depending on the method of administration. Where the compositions are in unit dose form, each dosage unit will preferably contain from 50-500 mg, of the drug. The dosage as employed for adult human treatment (average weight about 70 kg) will preferably range from 100 mg to 3 g per day, for instance 250 mg to 2 g of the drug per day, depending on the route and frequency of administration. Alternatively, the drug may be administered as part of the total dietary intake of a non-human animal. In this case the amount of drug employed may be less than 1% by weight of the diet and in preferably no more than 0.5% by weight. The diet for animals may consist of normal foodstuffs to which the drug may be added or the drug may be included in a premix for admixture with the foodstuff. A suitable method of administration of the drug to animals is to add it to

the non-human animal's drinking water. In this case a concentration of the drug in the drinking water of about 5-500 mg/ml, for example 5-200 mg/ml, is suitable.

The compounds of this invention are active against both Gram negative and Gram positive organisms, including *Bacteroides*, for instance *B. fragilis* BC1, *Haemophilus*, for instance *H. influenzae* Q1; *Moraxella*, for instance *M. catarrhalis* 1502; *Streptococci*, for instance *S. pyogenes* CN10 and *S. pneumoniae* PU7; *Staphylococci*, for instance *S. aureus* Oxford; *Escherichia*, for instance *E. Coli* DC0, *Legionella*, for instance *L. pneumophila*; *Pseudomonas*, for instance *P. aeruginosa* Dalgleish and *Enterobacter*, for instance *Ent. faecelis* I. In addition, compounds of this invention are active against *Staphylococci* organisms such as *S. aureus* and coagulase negative strains of *Staphylocci* such as *S. epidermidis* which are resistant (including multiply-resistant) to other anti-bacterial agents, for instance, β-lactam antibiotics such as, for example, methicillin; macrolides; aminoglycosides, and lincosamides. Compounds of the present invention are therefore useful in the treatment of MRSA, MRCNS and MRSE. Furthermore, compounds of the present invention are useful in the treatment of *Staphylococci* organisms which are resistant to mupirocin. Bacterial infections which may be treated include respiratory tract infections, otitis, meningitis, skin and soft tissue infections in man, mastitis in cattle, and respiratory infections in animals such as pigs and cattle. Accordingly, in a further aspect, the present invention provides a method of treating bacterial infection in human or non-human animals, which method comprises administering a therapeutically effective amount of a compound of formula (I) as hereinbefore defined, to a human or non-human animal in need of such therapy.

The compounds of this invention are also active against mycoplasma-induced infections, in particular infections caused by *Mycoplasma fermentans*, which has been implicated as a co-factor in the pathogenesis of AIDS. Accordingly in a further aspect, the present invention provides a method of treating humans infected with *M. fermentans*, in particular humans also infected with HIV, which method comprises treating humans in need of such therapy with an anti-mycoplasmal effective amount of a compound of formula (I).

Compounds of this invention also have antifungal activity. They may, for example, be used in treating fungal infections in man caused by, among other organisms, species of *Trichophyton*, *Trichosporon*, *Hendersonula*, *Microsporum*, *Epidermophyton*, *Candida*, *Cryptococcus*, *Saccharomyces*, *Paecilomyces* and *Pityrosporum*. They may also be used in the treatment of a variety of other fungal infections caused by, for example *Aspergillus*, *Coccidioides*, *Paracoccidioides*, *Histoplasma* and *Blastomyces* species. Accordingly, in a further aspect, the present invention provides for a method of treating fungal infections in animals, including

man, which method comprises treating a patient in need of antifungal therapy with an effect amount of a compound of formula (I).

No adverse toxicological effects are expected from the administration of a compound of formula (I).

Compounds of the present invention are also useful as herbicides and are active against a broad range of weed species, including monocotyledonous and dicotyledonous species. Many compounds show good selectivity in crops, particularly wheat, barley, maize, oil seed rape, sugar beet and rice. Compounds for use in hebicidal compositions of the present invention are preferably applied directly to unwanted plants (post-emergence application) but may also be applied to the soil before the unwanted plants emerge (pre-emergence application). Therefore, in a further aspect, the present invention provides for a process of severely damaging or killing unwanted plants which process comprises applying to the plants or the growth medium of the plants a herbicidally effective amount of a compound of formula (I), as hereinbefore defined.

For herbicidal use, compounds of the present invention are preferably used in the form of a composition further comprising a carrier which may be a liquid or solid diluent. Suitable such compositions may be dilute compositions which are ready for immediate use or concentrated compositions which are diluted prior to use, usually with water. Suitable liquid compositions may comprise a solution or a dispersion of the active ingredient in water, optionally with a surfactant, or may comprise a solution or a dispersion of the active ingredient in a water-immiscible organic solvent which is dispersed as droplets in water. Suitable solid compositions may be in the form of granules or dusting powders or dispersible powders or grains, further comprisng a wetting agent to facilitate dispersion. Suitable herbicidal formulating agents are well known in the art; see, for instance, WO 93/19599 (Zeneca Ltd).

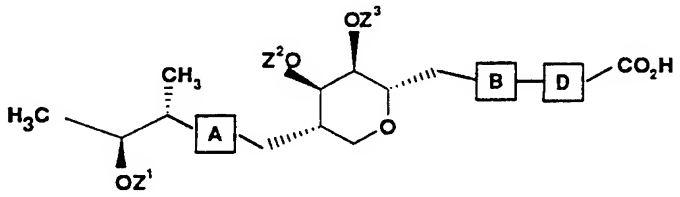
A suitable rate of application for herbicidal use will will depend upon the particular application but will usually be in the range 0.0001 to 20kg/hectare, preferably 0.001 to 10kg/hectare, more preferably 0.001 to 2kg/hectare.

Compounds of the present invention may be used alone or in admixture with other another herbicide which will preferably have a complementary herbicidal activity in the particular application. Suitable such complememtary herbicides are disclosed in WO 93/19599 (Zeneca Ltd).

Compounds of formula (I) may be readily obtained from known starting materials by adapting conventional synthetic procedures.

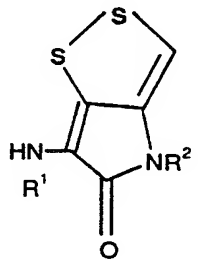
A suitable general process involves forming an amide bond between the terminal heterocyclic moiety and the remainder of the compound towards the end of the synthetic sequence.

Accordingly, the present invention provides a process for preparing a compound of formula (I) which process comprises reacting an acid of formula (IV):



(IV)

in which Z^1, Z^2 and Z^3, which may be the same or different, is each hydrogen or a hydroxyl protecting group, and A, B and D are as hereinbefore defined;
or an activated derivative thereof;
with an amine of formula (V):



(V)

in which R^1 and R^2 are as hereinbefore defined;
under amide forming conditions;
and thereafter removing any hydroxyl protecting groups.

Suitable amide forming conditions are well known to those skilled in the art and include, for instance, those described in Comprehensive Organic Synthesis, Pergamon Press, 1991, **6**, 381-417.

Particularly suitable amide forming conditions include reacting an activated derivative of an acid of formula (IV), for instance an acyl halide or a mixed anhydride such as an *iso*-butylcarbonic or methane sulphonic anhydride, with an amine of the formula (V) in the presence of a suitable base such as a tertiary amine, for instance pyridine, 2,6-lutidine or 4-dimethylaminopyridine, in an aprotic solvent such as chloroform, dichloromethane or tetrahydrofuran, at a moderate temperature, preferably in the range -30 to +30°C.

Suitable compounds of formula (IV) for use in preparing the compounds of formula (I) may be prepared by analogy with the processes described in our own earlier patent applications for similar derivatives *viz* EP 0 001 914-A, EP 0 029 665-A, WO 91/09855, WO 92/02518, WO 93/06118, EP 0 087 953-A, EP 0 123 378-A, EP 0 352 909-A, EP 0 399 645-A, WO 91/09856 and WO 94/02478 (Beecham Group or SmithKline Beecham), which are hereby incorporated herein by

reference. Such compounds of formula (IV) may usefully be regarded as novel examples of earlier derivatives having an appropriate substituent -DCO_2H, in which D is as hereinbefore defined. Thus, for instance, when D represents an oxyalkylene chain $O(CH_2)_n$, a useful starting point will be a hydroxy substituted analogue of an earlier monic acid derivative with the other hydroxy groups (corresponding to Z^1, Z^2 and Z^3) suitably protected. The isolated hydroxy group may then be alkylated with a suitable reagent $R^3(CH_2)_nCOR^4$ in which R^3 is a leaving group and R^4 is a carboxy protecting group. Alternatively, the moiety -DCOOH (in a suitably protected form, if need be) may be incorporated at an earlier stage of the sequence, by using an intermediate in which it is already present, prior to elaborating the spacer group B. It will be readily appreciated that, for other values of D, derivatives of monic acid with other functional groups may be used as a starting point.

Suitable starting materials for preparing compounds of formula (IV) in which B comprises a moiety -$C(CH_3)$=CH- attached to the tetrahydropyranylmethyl moiety include monic acids A and C, or activated derivatives thereof.

Compounds of formula (IV) are novel intermediates which are useful in the preparation of compounds of formula (I). Accoprdingly, in a further aspect, the present invention provides for a compound of formula (IV) as hereinbefore defined, excepting those intermediates which are specifically disclosed in earlier application WO 94/02478 (SmithKline Beecham plc).

Monic acid A may be readily obtained from pseudomonic acid A by the carefully controlled hydrolysis thereof, according to the process described in GB 1 587 058 (Beecham Group Ltd). A similar process may be used to obtain monic acid C from pseudomonic acid C (Clayton J P *et al*, J Chem Soc Perkin Trans I, 1982, 2827). Alternatively, monic acid C may be obtained from monic acid A by the deoxygenation thereof, as described by Clayton J P *et al*, J Chem Soc Perkin Trans I, 1982, 2827 and in EP 0 003 069-A (Beecham Group).

Amines of formula (V) may be prepared according to the processes described in GB 2 170 498-A (Imperial Chemical Industries plc) or by semi-synthetic processes starting from natural sources such as thiolutin and holomycin.

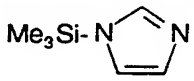
It will be readily appreciated that derivatives of monic acid A and monic acid C, such as the compounds of the present invention, are readily interconvertible by suitable deoxygenation (A→C) and epoxidation (C→A) procedures. In many instances, because of initial starting material availability, it will be more convenient, when preparing a compound of formula (I) in the "C" series, to start with a precursor in the "A" series and then at some convenient point in the synthesis convert this into the corresponding "C" series compound, by a suitable deoxygenation process; care being taken to ensure that the deoxygenating conditions selected are compatible with

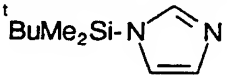
the remainder of the molecule

When used herein, the term 'hydroxyl-protecting group' refers to any such group known in the art which may be removed without disruption of the remainder of the molecule. Suitable hydroxyl-protecting groups are described in Protective Groups in Organic Synthesis, Greene and Wuts, Wiley-Interscience, New York, 2nd ed, 1991.

The hydroxyl groups of monic acids A and C, and compounds of formula (IV) may be protected at any stage of the above processes, using conventional methods. The hydroxyl-protecting group may be removed by methods known in the art, including enzymatic methods. Particularly suitable hydroxyl-protecting groups are silyl groups since these are readily removed under mild conditions. Such groups are introduced using conventional silylating agents, including halosilanes and silazanes, for example those of the following formulae :

L_3SiY; L_2SiY_2; L_3SiNL_2; $L_3SiNHSiL_3$; $L_3SiNHCOL$; $L_3SiO\text{-}C(L)=NSiL_3$; $L_3SiNHCONHSiL_3$; $LNHCONHSiL_3$; $^tBuMe_2Si\text{-}O\text{-}SO_2\text{-}CF_3$;





in which Me denotes methyl, t-Bu denotes t-butyl, Y is halogen and each group L is independently selected from hydrogen, $(C_1\text{-}6)$alkyl, $(C_1\text{-}6)$alkoxy, aryl or aryl$(C_1\text{-}4)$alkyl. A preferred silyating agent is trimethylsilyl chloride. Particularly suitable hydroxyl-protecting groups are trimethylsilyl, triethylsilyl and t-butyldimethylsilyl groups. Preferred hydroxyl-protecting groups are trimethylsilyl groups because of their ease of removal.

The glycol function of monic acids A and C and of the compounds of formula (IV) may be protected by forming a cyclic derivative using a compound of formula (VI):

$$R^cC(OR^d)(OR^e)(OR^f) \qquad (VI)$$

wherein R^c is hydrogen or $(C_1\text{-}6)$alkyl and each of R^d, R^e and R^f is $(C_1\text{-}6)$alkyl such that in the cyclic derivative Z^2 and Z^3 together are a moiety $R^cC(OR^d)$. Suitably R^c is hydrogen, methyl, ethyl, *n*- or *iso*-propyl; most suitably it is hydrogen. The groups R^d, R^e and R^f are suitably methyl, ethyl, *n*- or *iso*-propyl, or *n*-, *iso*-, *sec*- or t-butyl; most suitably methyl. The hydroxyl groups of a compound of formula (I) may also be protected prior to conversion to a further compound of formula (I) as described above. In each case the protecting groups described above may be removed by mild acid hydrolysis followed by alkaline hydrolysis, for instance, as described by Clayton J P *et al*, JCS Perkin Trans I, 1979, 308.

The following Examples illustrates the invention, but is not intended to limit the scope in any way:

Example 1 - 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-{4-(4-methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylbut-1-yloxyphenyl}but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 4-(4-carbomethoxybut-1-yloxy)benzaldehyde - A solution of *p*-hydroxybenzaldehyde (1.22g, 10mmol) in dry dimethyformamide (30ml) at 0°C under argon was treated with sodium hydride (60% dispersion in oil; 400mg, 10mmol). After 30 minutes methyl 5-bromovalerate (1.43ml, 10mmol) was added. The mixture was then warmed to 80°C for 6 hours and left to cool to room temperature (16 hours). The mixture was then diluted with water and extracted with ethyl acetate. The organic phase was washed with sodium carbonate solution, brine then dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica eluting with dichloromethane/ethyl acetate mixtures to give the title compound as a solid; δ_H ($CDCl_3$) 1.81-1.95 (4H, m, 2'-H_2, 3'-H_2), 2.38-2.48 (2H, t, *J* 6.9Hz, 4'-H_2), 3.67 (3H, s, CO_2Me), 4.08 (2H, t, *J* 5.9Hz, 1'-H_2), 6.99 (2H, d, *J* 8.7Hz, 3,5-H_2), 7.53 (2H, d, *J* 8.7Hz, 2,6-H_2); (Found: M^+, 236.1047. $C_{13}H_{13}O_4$ requires *M*, 236.1049).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-carbomethoxybut-1-yloxyphenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran - A solution of diisopropylamine (0.88ml, 6mmol) in dry THF (40ml) under argon at -30°C was treated dropwise with a solution of *n*-butyllithium in hexane (1.5M, 4ml, 6mmol). After 15 minutes the reaction mixture was cooled to -70°C and treated dropwise over 5 minutes with a solution of *tris*-trimethylsilylmonone* (2.59g, 5mmol) in THF (12ml). After 1 hour the mixture was treated with a solution of the product from (a) (1.18g, 5mmol) in THF (3ml). After a further one hour saturated ammonium chloride was added. The mixture was extracted with ethyl acetate and the organic phase washed with brine, then dried ($MgSO_4$) and evaporated. Chromatography on silica eluting with ethyl acetate/hexane mixtures gave the title compound (2.98g, 79%); δ_H ($CDCl_3$) *inter alia* 0.89 (3H, d, *J* 7.0Hz, 17-H_3), 1.22 (3H, d, *J* 6.3Hz, 14-H_3), 3.68 (3H, S, CO_2Me), 5.07-5.16 (1H, m, 1-H), 6.84 (2H, D, *J* 8.6Hz, 3',5'-H_2), 7.23-7.32 (2H, m, 2',6'-H_2); *m/z* (NH_3 DCI$^+$) 772 (MNH_4^+, 10%), 115 (100%).

*obtainable from 2S-acetonyl-3R,4R-dihydroxy-5S-(2S,3S-epoxy-5S hydroxy-4S-methylhexyl)-2,3,5,6-tetrahydropyran [GB 1 587 058, Beecham Group] by treatment thereof with trimethylsilyl chloride in the presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine in THF, by analogy with the protection step described in example 4(a)

c) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-carbomethoxybut-1-yloxyphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-

methylhexyl)tetrahydropyran - The product from (b) (2.9g, 3.85mmol) in benzene (140ml) was treated with manganese dioxide (4.35g) and refluxed with provision of azeotropic removal of water (Dean and Stark apparatus containing molecular sieves 4A) for 2½ hours. More manganese dioxide (1.45g) was added and heating continued for a further 2 hours. The mixture was diluted with dioxan and filtered through Kieselguhr, washing the pad well with dioxan. The filtrate was evaporated and the residue chromatographed on silica eluting with ethyl acetate/hexane mixtures to give the title compound (1.69g, 58%); δ_H ($CDCl_3$) *inter alia* 0.88 (3H, d, *J* 7.1Hz, 17-H_3), 1.21 (3H, d, *J* 6.1Hz, 14-H_3), 3.69 (3H, s, CO_2Me), 6.20 (1H, s, 2-H), 6.92 (2H, d, *J* 8.9Hz, 3',5'-H_2), 7.87 (2H, d, *J* 8.8Hz, 2',6'-H_2); *m/z* (NH_3DCI) 753 (MH^+, 5%), 90 (100%); (Found: M^+, 752.3862. $C_{37}H_{64}O_{10}Si_3$ requires *M* 752.3807). The ^1H spectrum indicated that the title compound was essentially in the enolic form.

d) 3R,4R-Dihydroxy-2S-[4-(4-carbomethoxybut-1-yloxyphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran - A solution of the product from (c) (1.6g, 2.12mmol) in THF (60ml) was treated with 0.4M HCl (12ml). After 2 min. saturated sodium hydrogen carbonate solution (1ml) was added. The mixture was then extracted with ethyl acetate and the organic phase washed with brine, dried ($MgSO_4$) and evaporated. Chromatography on silica eluting with dichloromethane/methanol mixtures gave the title compound (1.114g, 98%); υ_{max} (KBr) 3482, 1736, 1606, 1509, 1440cm^{-1}; λ_{max} (EtOH) 325nm (ε_m 22,970); δ_H ($CDCl_3$) *inter alia* 0.92 (3H, d, *J* 7.1Hz, 17-H_3), 1.21 (3H, d, *J* 6.3Hz, 14-H_3), 3.66 (3H, s, CO_2Me), 6.21 (1H, s, 2-H), 6.92 (2H, d, *J* 8.8Hz, 3',5'-H_2), 7.88 (2H, d, *J* 8.9Hz, 2',6'-H_2); δ_C ($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 21.6 (C-2"), 28.5 (C-3"), 31.7 (C-9), 33.6 (C-4"), 39.6 (C-8), 42.6 (C-4), 42.8 (C-12), 51.9 (C-6"), 55.7 (C-10), 61.3 (C-11), 66.0 (C-16), 67.6 (C-1"), 68.8 (C-6), 70.3 (C-7), 71.3 (C-13), 73.9 (C-5), 96.5 (C-2), 114.5 (C-3',5'), 126.7 (C-1'), 129.3 (C-2',6'), 162.7 (C-4'), 173.6 (C-5"), 182.9 (C-1), 194.0 (C-3); *m/z* (NH_3DCI) 537 (MH^+, 60%), 251 (100%). The ^1H spectrum indicated that the title compound was essentially in the enolic form.

e) 3R,4R-Dihydroxy-2S-[4-(4-carboxybut-1-yloxyphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran - Subtilisin Carlsberg (100mg) was dissolved in water (50ml) and the pH adjusted to 6.5 with 0.01M NaOH. The product from (d) (196mg, 0.36mmol) was added in one portion to the vigorously stirred mixture and the pH maintained at 6.5 by the addition of 0.01M NaOH. After 48 hours the clear solution was ultrafiltered and the filtrate evaporated to low volume and freeze-dried. The resulting amorphous solid was partitioned between ethyl acetate and water and, with vigorous stirring, the pH was adjusted to 2.5 with dilute H_2SO_4 (~0.01M). The organic phase was separated and dried ($MgSO_4$) to give the title compound (90mg, 48%); υ_{max} (KBr) 3414, 1719, 1603,

1509, 1458cm^{-1}; λ_{max} (EtOH) 326nm (ε_m 21,170), δ_H (d_4-MeOH) *inter alia* 0.94 (3H, d, *J* 7.1Hz, 17-H_3), 1.21 (3H, d, *J* 6.4Hz, 14-H_3), 6.32 (~1H, s, 2-H), 6.98 (2H, d, *J* 8.9Hz, 3',5'-H_2), 7.92 (2H, d, *J* 8.9Hz, 2',5'-H_2); *m/z* (NH_3DCI) 523 (*MH*$^+$, 10%), 74 (100%). The ^{1}H spectrum indicated that the title compound was essentially in the enolic form.

f) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-{4-(4-methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylbut-1-yloxyphenyl}but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran - A solution of the product from (e) (60mg, 0.115mmol) in THF (5ml) at 0°C under argon was treated sequentially with triethylamine (17.6µl, 0.126mmol) and *i*-butylchloroformate (15µl, 0.23mmol). After 30 minutes the mixture was treated with triethylamine (32µl, 0.23mmol) followed by 6-amino-4-methyl-1,2-thiolo-[4,3-b]-pyrrol-5(4H)-one hydrochloride (W.D. Celmer and I.A. Solomons, *J.Amer.Chem.Soc.*, 1955, 77, 2862) (33mg, 0.138mmol). After 3 h, further aliquots of triethylamine (11ml, 0.07mmol) and amine hydrochloride (11mg, 0.046mmol) were added. After a further h, the reaction mixture was diluted with ethyl acetate, washed with 5% citric acid, saturated sodium bicarbonate, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica eluting dichloromethane/methanol mixtures to give the title compound as a yellow solid (34mg, 45%); υ_{max} (KBr) 3410, 3034, 1658, 1600, 1532, 1507, 1438cm^{-1}; λ_{max} (EtOH) 385.5nm (ε_m 10,430), 324.5 (22,930); δ_H (d_4-MeOH containing <10% $CDCl_3$) *inter alia* 0.92 (3H, d, *J* 7.0Hz, 17-H_3), 1.20 (3H, d, *J* 6.4Hz, 14-H_3), 3.35 (3H, s, NMe), 6.28 (~1H, s, 2-H), 6.97 (2H, d, *J* 8.9Hz, 3',5'-H_2), 7.16 (1H, s, 3'''-H), 7.84 (2H, d, *J* 9.0Hz, 2',6'-H_2); *m/z* (FAB: thioglycerol) 691 (*MH*$^+$, 10%), 232 (100%). The ^{1}H spectrum indicated that the title compound was essentially in the enolic form.

Example 2 - N-(4-Methyl-1,2-dithiolo-[4,3-b]-5-(4H)-oxopyrrolo-6-yl)-monamide A

The title compound (7mg, 3%) was prepared from monic acid A (172mg) by the method described in example 1(f); υ_{max} (KBr) 3403, 2923, 1653, 1519, 1436cm^{-1}; δ_H (d_4-MeOH) 0.96 (3H, d, *J* 7.0Hz, 17-H_3), 1.20 (3H, d, *J* 6.4Hz, 14-H_3), 1.39 (1H, m, 12-H), 1.69 (2H, m, 9-H_2), 1.95 (1H, m, 8-H), 2.22 (3H, s, 15-H_3), 2.18-2.83 (4H, m, 4-H_2, 10-H, 11-H), 3.35 (3H, s, N-Me), 3.38-4.05 (6H, m, 5-H, 6-H, 7-H, 13-H, 16-H_2), 5.97 (1H, s, 2H), 7.23 (1H, s, 3'-H); *m/z* (EI$^+$) 512 (M$^+$).

Example 3 - 2-{6-(4-Methyl-1,2-dithiolo-[4,3-b]-5-(4H)-oxopyrrol-6-yl)]carbamoylhexoxy}-thiazol-5-yl-1-normon-2-yl ketone - A series

a) 2-(7,7,7-*tris*-methylthioheptoxy)-thiazole - 3,4-Dihydro-2H-pyran

(33.1mmol, 3.02ml) was added to 6-bromohexanol (27.65mmol, 5g) in 80ml diethyl ether. After 1.5 hours at room temperature a further portion of 3,4-dihydro-2H-pyran (33.1mmol, 3.02ml) was added and stirred for 2.5 hours. Saturated sodium hydrogen carbonate solution (100ml) was added, extraction with diethyl ether, drying ($MgSO_4$), evaporation to dryness under reduced pressure and purification by column chromatography over silica using dichloromethane/hexane (70-100%) as eluent gave 2-6-Bromohexyloxytetrahydropyran as a colourless oil (6.459g, 88%); δ_H ($CDCl_3$) 1.5-1.75 (8H, m, 4 x CH_2), 3.4-3.6 (4H, m, CH_2Br and CH_2O), 4.5 (1H, t, *J*2.8Hz, OC*H*O).

n-Butyllithium (1.6M in hexane) (29.24mmol, 19.5ml) was added dropwise to tris(methylthio)methane (24.37mmol, 3.24ml) in tetrahydrofuran (80ml) at -78°C. After 1.5 hours the above compound (24.37mmol, 6.459g) in THF (20ml) was added and stirred for 1 hour at -65°C. Saturated ammonium chloride solution (30ml) was added, extraction with diethyl ether, drying ($MgSO_4$), evaporation to dryness under reduced pressure and purification by column chromatography over silica using methanol/dichloromethane (0-20%) as eluent gave 7,7,7-trismethylthio-1-tetrahydropyran-2-yloxyheptane as a colourless oil (7.1124g, 86%); δ_H ($CDCl_3$) 2.1 (9H, s, 3 x SCH_3), 3.35-3.5 (2H, m, OCH_2), 3.7-3.9 (2H, m, cyclic OCH_2), 4.55 (1H, t, *J*2.8 Hz, O-C*H*-O).

Amberlyst-15(0.3g) was added to the above compound (20.98mmol, 7.11g) in methanol (150ml). After 4 hours filtered, evaporated to dryness under reduced pressure and purification by column chromatography over silica using diethyl ether/hexane (4%) as eluent gave 7,7,7-trismethylthio-heptanol as a colourless oil (3.73g, 70%); 1.2-1.9 (10H, m, 5 x CH_2), 2.1 (9H, s, 3 x SCH_3), 3.6 (2H, t, *J* 6.5Hz, OCH_2).

Sodium hydride (1.89mmol, 0.057g) was added to the above compound (2mmol, 0.508g) in THF (3ml). After 0.5 hours 2-bromothiazole (2.2mmol, 0.2ml) was added and the reaction heated at 40°C for 4 hours. Cooled, dilution with diethyl ether, filtered, evaporated to dryness under reduced pressure and purification by column chromatography over silica, using diethyl ether/hexane (0-10%) as eluent gave the title compound (0.232g, 34%); δ_H ($CDCl_3$) 1.3-1.9 (10H, m, 5 x CH_2), 2.1 (9H, s, 3 x SCH_3), 4.4 (2H, t, *J* 6.5Hz, OCH_2), 6.6 (1H, d, *J* 3.9Hz, 5-H), 7.1 (1H, d, *J* 3.8Hz, 4-H).

b) [2-(7,7,7-*tris*-methylthioheptoxy)-thiazol-5-yl]-1-(6,7,13-O-tristrimethylsilyl normon-2-yl) ketone A series - n-Butyllithium (1.6M in hexane) (2mmol, 1.25ml) was added dropwise to 2-(7,7,7-trismethylthioheptoxy)thiazole (2mmol, 0.674g) in THF (6ml) at -78°C. After 40 minutes N-methoxy-N-methyl-6,7,13-*O*-*tris*(trimethylsilyl) monamide (WO 93/06118, SmithKline Beecham plc)

(2mmol, 1.206g) in THF (10ml) was added dropwise. After 2 hours and warming to -50°C glacial acetic acid (4mmol, 0.2ml) was added followed by water (10ml). Extraction with diethyl ether, drying ($MgSO_4$), evaporation to dryness under reduced pressure and purification by column chromatography over silica using ethyl acetate/hexane (0-20%) as eluent gave the title compound (0.442g, 25%); δ_H ($CDCl_3$) 0.1-0.2 (27H, m, 9 x $SiCH_3$). 0.9 (3H, d, *J* 7.1 Hz,17-H_3), 1.2 (3H, d, *J* 6.3 Hz,14-H_3), 1.3-1.9 (10H, m, 5 x CH_2), 2.05 (9H, s, 3 x CH_3), 2.2 (3H, s, 15-H_3), 2.6 (2H, m, 10 and 11-H), 3.35 (1H, dd, *J* 2.9,8.9Hz, 6-H), 4.4 (2H, t, *J* 6.4Hz, OCH_2), 6.5 (1H, s, 2-H), 7.7 (1H, s, Ar-H).

c) **2-(7,7,7-*tris*-methylthioheptoxy)-thiazol-5-yl-1-normon-2-yl ketone - A series** - The product from Example 3(b) (0.5mmol, 0.439g) and hydrochloric acid (0.4M, 2.5ml) in THF (10ml) were stirred at room temperature for two minutes. Saturated sodium hydrogen carbonate was added, extraction with ethyl acetate, drying ($MgSO_4$), evaporation to dryness under reduced pressure and purification by column chromatography over silica using methanol/dichloromethane (0-7%) as eluent gave the title compound as a colourless oil (0.310g, 93%); υ_{max} (KBr) 2328, 1734, 1527, 1297, 838, 569cm^{-1}; λ_{max} (EtOH) 302nm (ε_m 17,227); δ_H (CD_3OD) 0.9 (3H, d, *J* 7.1Hz, 17-H_3), 1.2 (3H, d, *J* 6.6Hz, 14-H_3), 2.1 (9H, s, 3 x SCH_3), 2.25-2.35 (2H, m, 4-H_2), 2.65-2.8 (2H, m, 10 and 11-H), 3.4 (1H, dd, *J* 2.9, 9.0Hz, 6-H), 3.55 (1H, d, *J* 10.6Hz, 16"-H), 3.75-3.9 (4H, m, 5,7,13, 6-H), 4.45 (2H, t, *J* 6.4Hz, OCH_2), 6.7 (1H, s, 2-H), 7.9 (1H, s, Ar-H).

d) **2-(6-methoxycarbonylhexoxy)-thiazol-5-yl-1-normon-2-yl ketone - A series** - Mercury II oxide (3.38mmol, 0.072g) and Mercury II chloride (1.01mmol, 0.27g) were added to the product from Example 3(c) (0.338mmol, 0.224g) in methanol (6.3ml) at -40°C. After 55 minutes filtered through celite, washed with saturated ammonium chloride solution (10ml), extracted with dichloromethane (12ml), dried ($MgSO_4$), evaporated under reduced pressure and purification by column chromatography over silica using methanol/diethyl ether (0-4%) as eluent gave the title compound (0.113g, 60%); υ_{max} (KBr) 1646, 1479, 1258, 1187, 1055cm^{-1}; λ_{max} (EtOH) 302 (ε_m 20,224,); δ_H (CD_3OD) 0.95 (3H, d, *J* 7.1Hz, 17-H_3), 1.2 (3H, d, *J* 6.3Hz,14-H_3), 2.2 (3H, s, 15-H_3), 2.25-2.4 (3H, m, CH_2CO_2 and 4-H), 2.7-2.85 (3H, m, 4,10 and 11-H), 3.4 (1H, dd, *J* 2.7, 10.5Hz, 6-H), 3.55 (1H, d, *J* 10.5Hz, 16"-H), 3.6 (3H, s, CO_2CH_3), 3.75-3.9 (4H, m, 5,7,13 and 16-H), 4.45 (2H, t, *J* 6.5Hz, OCH_2), 6.7 (1H, s, 2-H), 7.9 (1H, s, Ar-H); *m/z* (E.I.) 569 (M^+, 50%), 83 (100%); (found: M^+ 569.2667, $C_{28}H_{43}NO_9S$ requires *M* 569.2659).

e) **2-(6-Carboxyhexoxy)-thiazol-5-yl-1-normon-2-yl ketone - A series** - Protease subtilisin Carlsberg (125mg) was added to a solution of the product from Example 3(d) (0.5mmol, 300mg) in acetone (30ml) and the mixture buffered with a

sodium hydrogen phosphate buffer (27mmol, 0.1m, 270ml, pH 7) to maintain a constant pH of 6.5. After stirring for 16.5 hours the volume was reduced and the reaction was washed with ether before being layered with ethyl acetate. The pH was adjusted to 3.5 using phosphonic acid (1.5M) and the aqueous layer extracted with ethyl acetate. the organic layer was washed with brine, dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give the title compound as a colourless gum, (0.247g, 89%). δ_H (d_4-MeOD), 0.96 (3H, d, *J* 7.1Hz, 17-H_3), 1.21 (3H, d, *J* 6.3Hz, 14-H_3), 1.24-2.08 (12H, m, 2"-H_2, 3"-H_2, 4"-H_2, 5"-H_2, 8-H, 9-H_2, 12-H), 2.23 (3H, s, 15-H_3), 2.25-2.35 (3H, m, 4-H, 6"-H_2), 2.72 (1H, dd, *J* 2.2, 7.5Hz, 11-H), 2.76 (1H, s, 4-H), 2.81 (1H, dt, *J* 2.3, 5.7Hz, 10-H), 3.38 (1-H, dd, *J* 3.0, 9.0Hz, 6-H), 3.55-3.60 (1H, m, 16-H), 3.70-3.90 (4H, m, 5-H, 7-H, 13-H, 16-H), 4.46 (2H, t, *J* 6.4Hz, 1"-H_2), 6.72 (1H, s, 2-H), 7.93 (1H, s, 4'-H).

f) 2-{6-(4-Methyl-1,2-dithiolo-[4,3-b]-5-(4H)-oxopyrrol-6-yl)carbamoyl-hexoxy}-thiazol-5-yl-1-normon-2-yl ketone - A series - The product from Example 3(d) (0.21mmol, 120mg) in dry tetrahydrofuran (20ml) under argon at 0°C was sequentially treated with triethylamine (0.23mmol, 0.032ml) and isobutylchloroformate (0.23mmol, 0.027ml). After 30 mins. the mixture was treated with triethylamine (0.29mmol, 0.041ml) followed by 6-amino-4-methyl-1,2-dithiolo-[4,3-b]-pyrrol-5(4H)-one hydrochloride (0.27mmol, 0.061g). After a further 24 hours the reaction was diluted with ethyl acetate, washed with aqueous sodium bicarbonate, brine, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The brown residue was purified by column chromatography eluting with 4% methanol in dichloromethane to give the title compound as a bright orange solid (77mg, 51%); λ_{max} (EtOH) 303nm (ε_m 20986); δ_H (d_6-acetone), 0.92 (3H, d, *J* 7.1Hz, 17-H_3), 1.17 (3H, d, *J* 6.3Hz, 14-H_3), 1.23-2.05 (12-H, m, 2"-H_2, 3"-H_2, 4"-H_2, 5"-H_2, 8-H, 9-H_2, 12-H), 2.23 (3H, d, *J* 0.9Hz, 15-H_3) 2.31-2.36 (1H, dd, *J* 9.3, 14.2Hz, 4-H), 2.46 (2H, t, *J* 7.3Hz, 6"-H), 2.70 (1H, dd, *J* 2.2, 7.4Hz, 11-H), 2.73 (1H, s, 4-H), 2.81 (1H, dt, *J* 2.2, 5.7Hz, 10-H), 3.24 (3H, s, N-C*H*$_3$), 3.40-3.45 (1H, m, 6-H), 3.55-3.60 (1H, m, 16-H), 3.64 (1H, s, -O*H*), 3.75-3.95 (4H, m, 5-H, 7-H, 13-H, 16-H, -O*H*), 4.50 (2H, t, *J* 6.7Hz, 1"-H), 6.76 (1H, s, 2-H), 7.09 (1H, s, 3"'-H), 7.93 (1H, s, 4'-H), 8.86 (1H, s, N-*H*); *m/z* (EI$^+$) 723 (*M*$^+$, 1%), 267 (5), 186 (100), and 128 (70).

Example 4 - 2-{6-(4-Methyl-1,2-dithiolo-[4,3-b]-5-(4H)-oxopyrrol-6-yl)carbamoylhexoxy}-thiazol-5-yl-1-normon-2-yl ketone - C series

a) N-Methoxy-N-methyl-6,7,13-O-*tris*(trimethylsilyl)monamide C - A solution of monic acid C (J.P. Clayton *et.al*, J.C.S. Perkin I, 1982, 2827) (4.10g, 12mmol) in THF (30ml) at 0°C was sequentially treated with triethylamine (1.83ml, 13.2mmol) and *i*-butylchloroformate (1.42ml, 12mmol). After 40 mins. the mixture

was diluted with ether, filtered and evaporated. The residue was dissolved in dichloromethane (30ml) and treated with a solution of N,-O-dimethylhydroxylamine (2.4mmol) in dichloromethane (10ml). After 1½h the mixture was washed with sodium bicarbonate solution, brine then dried ($MgSO_4$) and evaporated.

The residue was dissolved in THF (30ml) at 0° and sequentially treated with triethylamine (7.68ml, 55mmol), trimethylsilyl chloride (6.70ml, 53mmol) and DMAP (~2mg). After 20 hours at room temperature, the mixture was filtered washing the solid with hexane and the filtrate evaporated. The residue was dissolved in hexane washed with brine, dried and evaporated. The residue was chromatographed on silica eluting with ethyl acetate/hexane mixtures to give the title compound as an oil (2.3g, 32%); δ_H (d_4-MeOH), 0.97 (3H, d, *J* 7.1Hz, 17-H_3), 1.06 (3H, d, *J* 6.3Hz, 14-H_3), 2.16 (3H, s, 15-H_3), 3.20 (3H, s, NMe), 3.68 (3H, s, OMe), 5.30-5.50 (2H, m, 10-H, 11-H), 6.19 (1H, s, 2-H).

b) 2-(7,7,7-*tris*-methylthioheptoxy)-thiazol-5-yl-1-normon-2-yl ketone - C series - n-Butyllithium (1.1 M in hexane) (2.42mmol, 2.2ml) was added dropwise to 2-(7,7,7-trismethylthioheptoxy)thiazole (2.42mmol, 0.815g) in THF (6ml) at -78°C. After 40 minutes N-methoxy-N-methyl-6,7,13-*O-tris*(trimethylsilyl) monamide C (2.2mmol, 1.3g) in THF (10ml) was added dropwise. After 2 hours and warming to -50°C glacial acetic acid (4mmol, 0.2ml) was added followed by water (10ml). The mixture was extracted with ethyl acetate, dried ($MgSO_4$), and evaporated to dryness under reduced pressure .The residue was dissolved in THF (66ml) hydrochloric acid (0.4M, 13.2ml) was added and the mixture stirred at room temperature for two minutes. Saturated sodium hydrogen carbonate was added, extraction with ethyl acetate, drying ($MgSO_4$), evaporation to dryness under reduced pressure and purification by column chromatography over silica using methanol/dichloromethane (0-7%) as eluent gave the title compound as an amorphous solid (0.545g, 38%); δ_H ($CDCl_3$) 0.99 (3H, d, *J* 7.1Hz, 17-H_3), 1.15 (3H, d, *J* 6.3Hz, 14-H_3), 2.10 (9H, s, $(SMe)_3$), 2.26 (3H, s, 15-H_3), 5.35-5.55 (2H, m, 10-H, 11-H), 4.38-4.48 (2H, m, 1"-H_2), 6.60 (1H, s, 2-H), 7.75 (1H, s, 4'-H).

c) 2-(6-Methoxycarbonylhexoxy)-thiazol-5-yl-1-normon-2-yl ketone - C series - Mercury II oxide (0.8mmol, 0.173g) and Mercury II chloride (2.4mmol, 0.652g) were added to the product from Example 4(b) (0.8mmol, 0.545g) in methanol (20ml) at -40°C. After 55 minutes filtered through celite, washed with saturated ammonium chloride solution (10ml), extracted with dichloromethane (35ml), dried ($MgSO_4$), evaporated under reduced pressure and purification by column chromatography over silica using methanol/dichloromethane mixtures as eluent gave the title compound (0.353g, 80%) as an amorphous solid ; δ_H ($CDCl_3$) 0.98 (3H, d, *J* 7.1Hz, 17-H_3), 1.15 (3H, d, *J* 6.3Hz, 4H_3), 2.26 (3H, s, 15-H_3), 3.67 (3H, s,

CO_2Me), 4.40-4.45 (2H, m, 1"-H_2), 5.35-5.55 (2H, m, 10-H, 11-H), 6.60 (1H, s, 2-H), 7.75 (1H, s, 4'-H).

d) 2-(6-Carboxylatohexoxy)-thiazol-5-yl-1-normon-2-yl ketone - C series - A solution of the product from Example 4(c) (320mg, 0.6mmol) in THF (4ml) was treated with 2.5M sodium hydroxide solution (7.2ml). After 4h the stirred mixture was treated with a further aliquot (3.6ml) of sodium hydroxide. After 1 hour the mixture was evaporated to low volume, THF (4ml) and water (50ml) were added. After 10 mins. the mixture was washed with ethyl acetate, the aqueous phase was acidified to pH 2 with 5NHCl, saturated with brine and extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica eluting dichloromethane/methanol mixtures to give the title compound as a gum (81mg, 25%); δ_H (d_4-MeOH) 0.97 (3H, d, *J* 7.1Hz, 17-H_3), 1.08 (3H, d, *J* 6.3Hz, 14-H_3), 2.26 (3H, s, 15-H_3), 4.45-4.50 (2H, m, 1"-H_2), 5.40-5.45 (2H, m, 10-H, 11-H), 6.73 (1H, s, 2H), 7.93 (1H, s, 4'-H).

e) 2-{6-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl-hexoxy}-thiazol-5-yl-1-normon-2-yl ketone - C series - Using the method described in Example 3(f) the product from Example 4(d) (76mg, 0.14mmol) was converted to the title compound (38mg, 38%);υ_{max} (KBr) 3437, 2922, 1644, 1600 and 1229cm^{-1}; λ_{max} (EtOH) 304nm, (ε_m 19,518); δ_H (d_4-MeOH), 0.98 (3H, d, *J* 7.1Hz, 17-H_3), 1.09 (3H, d, *J* 6.3Hz, 14-H_3), 1.20-2.20 (12H, m, 2"-H_2, 3"-H_2, 4"-H_2, 5"-H_2, 8-H, 9-H_2, 12-H), 2.24 (3H, s, 15-H_3), 2.30-2.38 (1H, m, 4-H), 2.39-2.43 (1H, t, *J* 7.3Hz, 6"-H_2), 2.75-2.78 (1H, m, 4-H), 3.34 (3H, s, N-(CH_3), 3.39-3.42 (1H, dd, *J* 3.0, 9.2Hz, 6-H), 3.42-3.63 (1H, m, 16-H), 3.75-3.90 (4H, m, 5-H, 7-H, 13-H, 16-H), 4.46 (2H, t, *J* 6.4Hz, 1"-H_2), 5.40-5.45 (2H, m, 10-H, 11-H), 6.69 (1H, s, 2-H), 7.17 (1H, s, 3'"-H), and 7.86 (1H, s, 4'-H); δ_C (d_4-MeOH), 16.2 (C-17), 19.9 (C-15), 20.1 (C-14), 26.0 (C-4", C-5"), 27.8 (N-CH_3), 29.1 (C-2", C-3"), 33.3 (C-9), 35.0 (C-6"), 43.3 (C-8), 44.2 (C-4), 44.8 (C-12), 65.5 (C-16), 69.5 (C-6), 171.1 (C-7), 71.7 (C-13), 73.6 (C-1"), 75.8 (C-5), 112.4 (C-3'"), 115.0 (C-6a'"), 121.5 (C-2), 129.2 (C-11), 135.4 (C-10), 135.5 (C-5'), 136.2 (C-3a'"), 137.2 (C-6'"), 143.5 (C-4'), 159.4 (C-3), 166.3 (C-5), 173.6 (C-7"), 180.3 (C-2'), and 184.2 (C-1); *m/z* (EI^+) 707, (M^+, 1.25%), 446 (40), 186 (100) and 128 (75).

Example 5 - N-{8-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]octan-1-yl}monamide A

a) Triethylammonium N-(7-carboxyheptyl)monamide A - A solution of monic acid A (688mg, 2mmole) in THF (10ml) at -10°C under argon was treated sequentially with triethylamine (0.6ml, 4.4mmole) and isobutyl chloroformate (0.26ml, 2mmole). The mixture was stirred for 30 minutes and treated with

triethylamine (0.3ml, 2.2mmole) and 8-aminocaprylic acid (318mg, 2mmole) followed by enough water to give a clear solution. The mixture was stirred overnight at room temperature and evaporated. The residue was flash chromatographed on silica eluting with dichloromethane/methanol mixtures to give the title compound (710mg, 61%) as a mixture with triethylammonium monate A; δ_H (250MHz, CD_3OD, Me_4Si) *inter alia* 0.95 (3H, d, *J* 7Hz, 17-H_3), 1.20 (3H, d, *J* 6.4Hz, 14-H_3), 1.33 (9H, t, *J* 6.4Hz, 3 x CH_3), 1.35-1.72 (13H, m, 5 x CH_2, 9-H_2, 12-H), 1.95 (1H, m, 8-H), 2.13 (3H, s, 15-H_3), 2.10-2.68 (4H, m, CH_2CO, 4-H_2), 2.68-2.86 (2H, m, 10-H, 11-H), 3.20 (6H, q, *J* 6.4Hz, 3 x NCH_2), 3.15-3.92 (8H, m, N-CH_2, 5-H, 6-H, 7-H, 13-H, 16-H_2), 5.73 (1H, s, 2-H).

b) N-{8-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]octan-1-yl}monamide A - A solution of the product from Example 5(a) (370mg), in THF (10ml) at -10°C under argon was treated sequentially with triethylamine (0.12ml) and isobutyl chloroformate (0.1ml). After 20 minutes the mixture was treated with triethylamine (0.12ml) and 6-amino-4-methyl-1,2-dithiolo-[4,3-b]-pyrrol-5-(4H)-one hydrochloride (165mg) followed by enough water to give a clear solution. The mixture was stirred at room temperature for 2 hours, diluted with ethyl acetate, washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was flash chromatographed on silica eluting with dichloromethane/methanol mixtures to give the title compound (102mg, 25%); υ_{max} (KBr) 3415 (br), 2928, 1653, 1531cm^{-1}; λ_{max} (EtOH) 390 (ε_m 10,489), 312.5 (ε_m 4,216); δ_H (250MHz, CD_3OD, Me_4Si), 0.94 (3H, d, *J* 7Hz, 17-H_3), 1.20 (3H, d, *J* 6.4Hz, 14-H_3), 1.28-1.72 (13H, m, 5 x CH_2, 9-H_2, 12-H), 1.96 (1H, m, 8-H), 2.12 (3H, s, 15-H_3), 2.10, 2.61 (2H, 2 x m, 4-H_2), 2.38 (2H, t, *J* 7.3Hz, 2'-H_2), 2.68-2.82 (2H, m, 10-H, 11-H), 3.18 (2H, t, *J* 6.8Hz, 8'-H_2), 3.35 (3H, s, NMe), 3.33-3.94 (6H, m, 5-H, 6-H, 7-H, 13-H, 16-H_2), 5.73 (1H, s, 2-H), 7.25 (1H, s, 3"-H); δ_C (CD_3OD); 17.25 (C-17), 18.80 (C-15), 20.31 (C-14), 26.58, 27.63, 29.99, 30.06, 30.36 (C-3', C-4', C-5', C-6', C-7'), 28.02 (C-NCH_3), 32.99 (C-9), 36.52 (C-2'), 40.03 (C-8'), 41.63 (C-8), 43.64 (C-4), 43.71 (C-12), 56.69 (C-10), 61.25 (C-11), 66.30 (C-16), 70.06 (C-6), 70.70 (C-13), 71.60 (C-7), 76.22 (C-5), 112.87 (C-3"), 115.38 (C-6a"), 121.28 (C-2), 135.94 (3a"), 137.56 (C-6"), 151.64 (C-3), 168.60 (C-5"), 169.66 (C-1), 174.21 (C-1'); *m/z* (EI) (Found M^+ 653.2814, $C_{31}H_{47}N_3O_8S_2$ requires M 653.2805).

Example 6 - N-{8-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]octan-1-yl}monamide C

a) Triethylammonium N-(7-carboxyheptyl)monamide C - Prepared as described in Example 5(a) from the mixed anhydride of monic acid C and 8-aminocaprylic acid in 30% yield; δ_H (250MHz, CD_3OD, Me_4Si) *inter alia* 0.99 (3H,

d, *J* 7Hz, 17-H_3), 1.09 (3H, d, *J* 6.4Hz, 14-H_3), 1.31 (9H, t, *J* 7.3Hz, 3 x CH_3), 1.25-1.70 (13H, m, 5 x CH_2, 9-H_2, 12-H), 1.76 (1H, m, 8-H), 2.10-2.70 (7H, m, 2'-H_2, 4-H_2, 15-H_3), 3.20 (6H, q, *J* 7.3Hz, 3 x CH_2), 3.20-3.87 (8H, m, 5-H, 6-H, 7-H, 13-H, 16-H_2, 8'-H_2), 5.43 (2H, m, 10-H, 11-H), 5.74 (1H, s, 2-H).

b) **N-{8-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]octan-1-yl}monamide C** - Prepared as described in Example 5(b) from the mixed anhydride of Example 6(a) and 6-amino-4-methyl-1,2-dithiolo-[4,3-b]-pyrrol-5(4H)one hydrochloride in 17% yield; υ_{max} (KBr) 3412 br, 2925, 1657, 1532cm^{-1}; λ_{max} (EtOH) 389.5 (ε_m 9,546), 310 (ε_m 3,836); δ_H (250MHz, CD_3OD, Me_4Si), 0.99 (3H, d, *J* 6.9Hz, 17-H_3), 1.09 (3H, d, *J* 6.3Hz, 14-H_3), 1.27-1.83 (14H, m, 5 x CH_2, 8-H, 9-H_2, 12-H), 2.13 (3H, s, 15-H_3), 2.15 and 2.61 (2H, 2 x m, 4-H_2), 2.38 (2H, t, *J* 7.3Hz, 2'-H_2), 3.18 (2H, t, *J* 7Hz, 8'-H_2), 3.36 (3H, s, NCH_3), 3.43-3.87 (6H, m, 5-H, 6-H, 7-H, 13-H, 16-H_2), 5.44 (2H, m, 10-H, 11-H), 5.74 (1H, s, 2-H), 7.26 (1H, s, 3"-H); *m/z* (EI) (Found M^+ 637.2851. $C_{31}H_{14}N_3O_7S_2$ requires 637.2855).

Example 7 - 5-(4-(3-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylprop-1-oxy)phenyl)-2-(1-normon-2-yl)oxazole A

a) Aminomethyl 4-hydroxyphenyl ketone hydrochloride - 4'-Hydroxyacetophenone (13.62g, 100mmol) was dissolved in dry dichloromethane (200ml), triethylamine (16ml, 115mmol) added, and the mixture cooled in an ice bath before adding chlorotrimethylsilane (13.3ml, 105mmol). Stirred for ½h then triethylamine (16.7ml, 120mmol) was added, followed by trimethylsilyltriflate (21.3ml, 110mmol). Stirred for ½h, then N-bromosuccinimide (18.69g, 105mmol) was added. After stirring for 1h, water (160ml) and 5N hydrochloric acid (40ml) were added, and the mixture stirred vigorously for ¼h. The phases were separated, and the organic washed with aqueous sodium metabisulphite and brine, dried and evaporated. The crude product was partially purified by chromatography to give an off-white solid (15.69g). N.m.r. showed this to be a mixture of starting material and the required bromomethyl 4-hydroxyphenyl ketone.

This material was dissolved in acetone (100ml), diluted with water (30ml), and sodium azide (4.73g, 73mmol) added. The mixture was stirred for 4½h, reduced in volume *in vacuo*, diluted with water and extracted with ethyl acetate (x2). The combined organic extracts were washed with brine, dried and evaporated to give a pale brown solid (14.29g), which was partially purified by chromatography, eluting with 20-40% ethyl acetate in hexane, to give an off-white solid (12.99g); υ_{max} (KBr) 3304, 2104, 1661, 1573, and 1165cm^{-1}; ^1H n.m.r. showed the product to be a mixture of the required azide and 4'-hydroxyacetophenone; *m/z* 178 (MH^+, 5%), 177

(M^+, 4%), 170 (5), 136 (M^+, 40), 122 (81), 121 (100), and 93 (99).

This material was dissolved in ethanol (130ml), water (40ml) and 5N hydrochloric acid (25ml), and the mixture hydrogenated over 10% palladium on charcoal catalyst (1.0g). Further portions of catalyst were added at intervals. After 3h hydrogenation the catalyst was filtered off, washed with water, and the solution evaporated to dryness. The resulting residual powder was stirred vigorously with diethyl ether, and the required product filtered off and dried *in vacuo* to give a buff powder (6.583g, 35%); υ_{max} (KBr) 3424, 3055, 1673, 1602, and 1488cm^{-1}; δ_H ($(CD_3)_2SO$) 4.45 (2H, s, CH_2), 6.95 (2H, d, *J* 8.7Hz, 2 x Ar-H), 7.89 (2H, d, *J* 8.7Hz, 2 x Ar-H), 8.38 (3H, br.s, -N^+H_3), and 10.86 (1H, s, OH); δ_H (D_2O) 4.60 (2H, s, CH_2), 6.96 (2H, d, *J* 8.7Hz, 2 x Ar-H), and 7.90 (2H, d, *J* 8.7Hz, 2 x Ar-H); *m/z* 152 (*M*-Cl, 12%), 151 M^+-HCl, 73), 121 (100), and 93 (92). (Found: M^+, 151.0639. $C_8H_9NO_2$ requires *M*, 151.0634); Found: C, 49.89; H, 5.43; N, 7.38%. $C_8H_{10}ClNO_2$ requires: C, 51.21; H, 5.37; N, 7.47%.

b) **N-[2-(4-Hydroxyphenyl)-2-oxoethyl]monamide A** - Monic acid A (3.44g, 10mmol) was dissolved in dry tetrahydrofuran (100ml) and triethylamine (1.53ml, 11mmol), cooled in an ice bath and treated with isobutylchloroformate (1.30ml, 10mmol). The mixture was stirred for ½h, then aminomethyl 4-hydroxyphenyl ketone hydrochloride (2.064g, 11mmol) in THF:water (1:2, 15ml) was added, followed by triethylamine (3.48ml, 25mmol). The mixture went dark purple, and was stirred for 1h with cooling, before reducing in volume *in vacuo*. This caused most of the crude product to precipitate as a purple oil. The remainder of the product was extracted out with ethyl acetate, and methyl isobutyl ketone. The combined products were evaporated, then redissolved in methanol, pre-absorbed onto silica, and purified by column chromatography eluting with 0-12% methanol in dichloromethane, to give the title compound as an orange foam (2.680g, *ca.*56%); υ_{max} (KBr) 3405, 1678, 1659, 1627, 1603, and 1230cm^{-1}; λ_{max} (EtOH) 220 (ε_m 25,041) and 279nm (16,898); δ_H (CD_3OD) (*inter alia*) 0.92 (3H, d, *J* 7.1Hz, 17-H_3), 1.18 (3H, d, *J* 6.4Hz, 14-H_3), 2.14 (3H, s, 15-H_3), 4.63 (2H, s, 1'-H_2), 5.88 (1H, s, 2-H), 6.80-6.87 (2H, m, 2 x Ar-H), and 7.84-7.91 (2H, m, 2 x Ar-H) (n.m.r. also showed a trace of CH_3OH and triethylamine hydrochloride); *m/z* (NH_3, DCI) 478 (MH^+, 58%), 91 (100), and 74 (100).

c) **5-(4-Hydroxylphenyl)-2-(1-normon-2-yl)oxazole A** - N-[2-(4-Hydroxyphenyl)-2-oxoethyl]monamide A (2.60g, 5.4mmol) was suspended in dry dichloromethane (100ml), cooled in an ice bath and treated sequentially with pyridine (5.3ml, 65mmol), trichloroacetyl chloride (6.8ml, 54mmol) and 4-dimethylaminopyridine (catalytic). After stirring for 1½h, the mixture was reduced in volume, diluted with ethyl acetate, and washed with water, 5% aqueous citric acid,

aqueous sodium hydrogen carbonate (x2), and brine, dried and evaporated to give an orange foam.

This material was dissolved in methanol (60ml), cooled and potassium carbonate (3.38g, 24.5mmol) added. After stirring for 1½h the mixture was reduced in volume, diluted with water and extracted with ethyl acetate (x3). The combined organic extracts were dried and preabsorbed onto silica. Chromatography, eluting with 0-6% methanol in dichloromethane, afforded the title compound as an off-white powder (2.363g, 94%); υ_{max} (KBr) 3386, 3260, 2971, 1651, 1616, 1252, and 836cm^{-1}; λ_{max} (EtOH) 204 (ε_m 14,870), 238 (7,144), and 309nm (20,693); δ_H (CD_3OD) (*inter alia*) 0.95 (3H, d, *J* 7.0Hz, 17-H_3), 1.20 (3H, d, *J* 6.4Hz, 14-H_3), 2.29 (3H, s, 15-H_3), 6.22 (1H, s, 2-H), 6.80-6.90 (2H, m, 2 x ArH), 7.28 (1H, s, 4'-H), and 7.48-7.58 (2H, m, 2 x ArH); δ_C (CD_3OD) 12.2 (C-17), 19.6 (C-15), 20.2 (C-14), 32.9 (C-9), 41.5 (C-8), 43.6 (C-12), 43.7 (C-4), 56.8 (C-10), 61.2 (C-11), 66.3 (C-16), 69.9 (C-6), 70.6 (C-7), 71.5 (C-13), 76.4 (C-5), 113.6 (C-2), 116.8 (C-3", C-5"), 120.6 (C-4'), 120.8 (C-1"), 126.7 (C-2", C-6"), 148.0 (C-5'), 152.0 (C-3), 159.1 (C-4"), and 161.7 (C-2'); *m/z* 459 (M^+, 6%), 244 (8), and 215 (100). (Found: M^+, 459.2264. $C_{25}H_{33}NO_7$ requires *M*, 459.2258).

d) 5-[4-(3-Carboxyprop-1-oxy)phenyl]-2-(1-normon-2-yl)oxazole A - Sodium hydride (60% in oil, 0.040g, 1mmol) was suspended in dry dimethylformamide (5ml) under argon, then 5-(4-Hydroxyphenyl)-2-(1-normon-2-yl)oxazole A (0.460g, 1mmol) in DMF (7ml) was added. The mixture was stirred for ½h, then (3,4,5,6-tetrahydropyran-2-yl) 4-bromobutanoate (0.251g, 1mmol) in DMF (3ml) was added. After stirring for 24h the mixture was reduced in volume *in vacuo*, diluted with aqueous sodium hydrogen carbonate and extracted with ethyl acetate (x2). The combined organic extracts were washed with brine, dried and evaporated. The crude product was separated by column chromatography, eluting with 0-8% methanol in dichloromethane, to give (a) the tetrahydropyranyl ester as a white foam (0.190g, 30%) and (b) recovered starting material (0.175g, 38%). The tetrahydropyranyl ester (0.185g, 0.29mmol) was dissolved in methanol (5ml) and water (4ml), and glacial acetic acid (1 drop) added. The mixture was stirred for 3¾h, then diluted with aqueous sodium hydrogen carbonate and washed with diethyl ether. The aqueous phase was then layered with ethyl acetate and adjusted to pH 3.5 with 1.5M phosphoric acid. The phases were separated, and the aqueous extracted with ethyl acetate (x2). The combined ethyl acetate layers were washed with brine, dried and evaporated to give a white foam (0.155g, 28% overall); υ_{max} (KBr) 3435, 2924, 1719, 1500, and 1251cm^{-1}; λ_{max} (EtOH) 240 (ε_m 8,461) and 308nm (25,210); δ_H (CD_3OD) (*inter alia*) 0.95 (3H, d, 17-H_3), 1.2 (3H, d, 14-H_3), 2.3 (3H, s, 15-H_3), 2.5 (2H, t, 3'-H_2), 4.08 (2H, t, 1'-H_2), 6.25 (1H, s, 2-H), 7.0-7.1 (2H, m, 2 x ArH),

7.35 (1H, s, 4'-H), and 7.6-7.7 (2H, m, 2 x ArH); *m/z* 545 (M^+, 15%), 527 (5), 301 (6), 215 (70), 121 (85), and 43 (100). (Found: M^+, 545.2627. $C_{29}H_{39}NO_9$ requires *M*, 545.2625).

e) **5-(4-(3-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylprop-1-oxy)phenyl)-2-(1-normon-2-yl)oxazole A** - 5-[4-(3-Carboxyprop-1-oxy)phenyl]-2-(1-normon-2-yl)oxazole A (0.140g, 0.26mmol) was dissolved in dry tetrahydrofuran (10ml) and triethylamine (0.04ml, 0.29mmol), cooled in an ice-bath, and treated with isobutyl chloroformate (0.034ml, 0.26mmol). The mixture was stirred for ½h, then triethylamine (0.047ml, 0.34mmol) was added, followed by 6-amino-4-methyl-1,2-dithiolo-[4,3-b]-pyrrol-5(4H)-one hydrochloride (0.070g, 0.31mmol). The mixture was stirred at room temperature for 22½h, by which time precipitation had occurred. The reaction was diluted with methanol and dichloromethane and pre-absorbed onto silica before column chromatography, eluting with 0-8% methanol in dichloromethane. This gave the product (0.150g) still slightly impure. Therefore it was triturated with dichloromethane to give the title compound as a yellow powder (0.106g, 57%), m.p.163-164°C; υ_{max} (KBr) 3420, 3262, 1681, 1660, 1652, and 1527cm^{-1}; λ_{max} (EtOH) 238 (ε_m 11,628), 309 (25,018), and 392nm (8,457); δ_H ($CD_3OD/CDCl_3$) 0.95 (3H, d, *J* 7.0Hz, 17-H_3), 1.22 (3H, d, *J* 6.4Hz, 14-H_3), 1.38-1.48 (1H, m, 12-H), 1.62-1.81 (2H, m, 9-H_2), 1.92-2.02 (1H, m, 8-H), 2.10-2.22 (2H, m, 2"-H_2), 2.30 (3H, s, 15-H_3), 2.35 (1H, dd, *J* 14.8, 9.5Hz, 4-H), 2.62 (2H, t, *J* 7.3Hz, 3"-H_2), 2.7-2.9 (3H, m, 4-H, 10-H, 11-H), 3.37 (3H, s, NCH_3), 3.43 (1H, dd, *J* 3.0, 8.9Hz, 6-H), 3.60 (1H, br.d, *J* 10.4Hz, 16-H), 3.75-3.93 (4H, m, 5,7,13,16-H), 4.11 (2H, t, *J* 6.0Hz, 1"-H_2), 6.25 (1H, s, 2-H), 6.98 (2H, d, *J* 9.9Hz, 2 x ArH), 7.10 (1H, s, 4'-H), 7.24 (1H, s, 3'"-H), and 7.57 (2H, d, *J* 9.9Hz, 2 x ArH); *m/z* (NH_3, DCI) 714 (MH^+, 7%), 91 (54), and 74 (100); *m/z* (Electrospray) 736 (MNa^+, 5%), 714 (MH^+, 18), and 169 (100).

Example 8 - 5-[4-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylmethyloxy-phenyl]-2-(1-normon-2-yl)oxazole A

a) **5-(4-Methoxycarbonylmethyloxyphenyl)-2-(1-normon-2-yl)oxazole A** - 5-(4-Hydroxyphenyl)-2-(1-normon-2-yl)oxazole A (1.011g, 2.2mmol) (example 7c) was dissolved in dry dimethylformamide (12ml), and 1,1,3,3-tetramethylguanidine (0.30ml, 2.4mmol) was added. The mixture was stirred for five minutes then methyl bromoacetate (0.23ml, 2.4mmol) was added. After stirring for 16h some starting material remained, therefore further portions of 1,1,3,3-tetramethylguanidine (0.083ml, 0.66mmol) and methyl bromoacetate (0.062ml, 0.66mmol) were added twice. Stirred for a further hour, then diluted with aqueous sodium hydrogen carbonate and extracted with ethyl acetate (x2). The combined organic extracts were

washed with brine, dried and evaporated. The product was purified by column chromatography, eluting with 0-8% methanol in dichloromethane, to give the title compound as a white foam (0.751g, 64%); υ_{max} (KBr) 3420, 2923, 1759, 1499, and 1213cm^{-1}; λ_{max} (EtOH)236 (ε_m 8,900) and 306nm (28,297); δ_H (CD_3OD) (*inter alia*) 0.96 (3H, d, *J* 7.1Hz, 17-H_3), 1.21 (3H, d, *J* 6.5Hz, 14-H_3), 2.31 (3H, s, 15-H_3), 3.81 (3H, s, CO_2CH_3), 4.78 (2H, s, 1"-H_2), 6.25 (1H, s, 2-H), 6.98-7.1 (2H, m, 2 x ArH), 7.38 (1H, s, 4'-H), and 7.61-7.71 (2H, m, 2 x ArH); *m/z* 531 (M^+, 10%) and 287 (100). (Found: M^+, 531.2469. $C_{28}H_{37}NO_9$ requires *M*, 531.2468).

b) 5-(4-Carboxymethyloxyphenyl)-2-(1-normon-2-yl)oxazole A - 5-(4-Methoxycarbonylmethyloxyphenyl)-2-(1-normon-2-yl)oxazole A (0.250g, 0.47mmol) was dissolved in acetone (25ml), and disodium hydrogen phosphate buffer solution (0.1M, pH 7, 225ml) added, followed by Subtilisin Carlsberg enzyme (0.125g). This clear solution was stirred for 66h, then reduced in volume *in vacuo*, washed with ether (75ml), layered with ethyl acetate, and adjusted to pH 3.5 with 1.5M phosphoric acid. The mixture was filtered through celite, the phases separated, and the aqueous extracted with ethyl acetate (x2) with further filtering. The combined organic extracts were washed with brine, dried and evaporated to give a colourless gum (0.255g, >100%); δ_H (CD_3OD) (*inter alia*) 0.96 (3H, d, *J* 7.1Hz, 17-H_3), 1.21 (3H, d, *J* 6.4Hz, 14-H_3), 2.31 (3H, s, 15-H_3), 4.72 (2H, s, 1"-H_2), 6.25 (1H, s, 2-H), 7.04 (2H, d, J 8.9Hz, 2 x ArH), 7.38 (1H, s, 4'-H), and 7.65 (2H, d, *J* 8.9Hz, 2 x ArH); *m/z* 517 (M^+, 2%), 273 (28), 91 (87), and 69 (100). (Found: M^+, 517.2308. $C_{27}H_{35}NO_9$ requires *M*, 517.2311).

c) 5-[4-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylmethyl-oxyphenyl]-2-(1-normon-2-yl)oxazole A - The title compound was prepared using the method described in Example 7e. The product was an orange solid (0.24g, 78%); υ_{max} (KBr) 3372, 2922, 1653, 1616, and 1497cm^{-1}; λ_{max} (EtOH) 307 (ε_m 31,503) and 393nm (11,405); δ_H ($CD_3OD/CDCl_3$) 0.93 (3H, d, *J* 7.1Hz, 17-H_3), 1.19 (3H, d, *J* 6.5Hz, 14-H_3), 1.34-1.46 (1H, m, 12-H), 1.67-1.79 (2H, m, 9-H_2), 1.9-2.05 (1H, m, 8-H), 2.28 (3H, s, 15-H_3), 2.27-2.39 (1H, m, 4-H), 2.67-2.84 (3H, m, 4-H, 10-H, 11-H), 3.37 (3H, s, NCH_3), 3.35-3.45 (1H, m, 6-H), 3.57 (1H, br.d, *J* 11.6Hz, 16-H), 3.71-3.97 (4H, m, 5,7,13, 16-H), 4.69 (2H, s, 1"-H_2), 6.22 (1H, s, 2-H), 7.05-7.15 (2H, m, 2 x ArH), 7.21 (1H, s, 4'-H), 7.28 (1H, s, 3'''-H), and 7.59-7.69 (2H, m, 2 x ArH); *m/z* (NH_3, DCI), 686 (MH^+, 7%) and 74 (100).

Example 9 - 3R,4R-Dihydroxy-2-S-[2,4-dioxo-4-{4-[3-(4-methyl-1,2-thiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbomoylprop-1-yloxy]phenyl}but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) **4-(3-carbomethoxyprop-1-yloxy)benzaldehyde** - Using the method described in Example 1a, p-hydroxybenzaldehyde (1.22g, 10mmol) was reacted with methyl 4-bromobutyrate (1.81g, 10mmol) to give the title compound (1.37g, 61%) as a light yellow solid; δ_H ($CDCl_3$) 2.16 (2H, m, 2'-H), 2.58 (2H, t, *J* 7.1Hz, 3'-H_2), 3.72 (3H, s, CO_2Me), 4.11 (2H, t, *J* 6.0Hz, 1'-H_2), 6.95 (2H, d, *J* 8.7Hz, 3, 5-H_2), 7.88 (2H, d, *J* 8.7Hz, 2, 6-H_2). (Found: M^+, 222.0888. $C_{12}H_{14}O_2$ requires *M* 222.0892).

b) **3R,4R-Bistrimethylsilyloxy-2S-[4-{4-(3-carbomethoxyprop-1-yloxy)phenyl}-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)-tetrahydropyran** - Using the method described in Example 1b, the product from Example 9a (1.11g, 5mmol) was reacted with tristrimethylsilyl monone (2.59g, 5mmol) to give the title compound (0.9g); δ_H ($CDCl_3$) *inter alia* 0.88 (3H, d, *J* 7.0Hz, 17-H_3), 1.21 (3H, d, *J* 6.3Hz, 14-H_3), 3.69 (3H, s, CO_2Me), 5.05-5.17 (1H, m, 1-H), 6.85 (2H, d, *J* 8.6Hz, 3', 5'-H_2), 7.21-7.28 (2H, m, 2', 6'-H_2).

c) **3R,4R-Bistrimethylsilyloxy-2S-[4-{4-(3-carbomethoxyprop-1-yloxy)phenyl}-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)-tetrahydropyran** - Using the method described in Example 1c, the product from Example 9b, (3.6g, 4.86mmol) was oxidised with manganese dioxide (5.4g, 1.8g) to give the title compound (1.77g, 47%); δ_H ($CDCl_3$) *inter alia* 0.88 (3H, d, *J* 7.1Hz, 17-H_3), 1.22 (3H, d, *J* 6.1Hz, 14-H_3), 3.70 (3H, s, CO_2Me), 6.21 (1H, s, 2-H), 6.93 (2H, d, *J* 8.7Hz, 3', 5'-H_2), 7.85 (2H, d, *J* 8.7Hz, 2', 6'-H_2); *m/z* (EI) 739 (MH^+, 75%), 90 (100%). The ^1H spectrum indicated that the title compound was essentially in the enolic form.

d) **3R,4R-Dihydroxy-2S-[4-{4-(3-carbomethoxyprop-1-yloxy)phenyl}-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran** - Using the method described in Example 1d, the product from Example 9c (1.0g) was converted to the title compound (780mg); δ_H ($CDCl_3$) *inter alia* 0.92 (3H, d, J 7.0Hz, 17-H_3), 1.22 (3H, d, *J* 6.2Hz, 14-H_3), 3.71 (3H, s, CO_2Me), 6.21 (1H, s, 2-H), 6.93 (2H, d, *J* 9.0Hz, 3', 5'-H_2), 7.86 (2H, d, *J* 8.9Hz, 2', 6'-H_2). The 'H spectrum indicated that the title compound was essentially in the enolic form.

e) **3R,4R-Dihydroxy-2S-[4-{4-(3-carboxyprop-1-yloxy)phenyl}-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran** - Using the method described in Example 1e, the product from Example 9d (300mg) was treated with Subtilisin Carlsberg (150mg) to give the title compound (133mg, 91%); λ_{max} (EtOH) 323nm (ε_m 20,110); δ_H (d_4-MeOH) *inter alia* 0.92 (3H, d, *J* 7.1Hz, 17-H_3), 1.20 (3H, d, *J* 6.3Hz, 14-H_3), 6.34 (~1H, s, 2-H), 6.99 (2H, d, *J* 8.9Hz, 3', 5'-H_2), 7.92 (2H, d, *J* 8.9Hz, 2', 6'-H_2); *m/z* (Electrospray) 509 (MH^+, 100%). The 'H spectrum indicated that the title compound was essentially in the enolic form.

f) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-{4-[3-(4-methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylprop-1-yloxy]phenyl}but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran - Using the method described in Example 1f, the product from Example 9e (130mg) was converted to the title compound (60mg, 34%); ν_{max} (KBr) 3420, 3261, 1676, 1645, 1589cm^{-1}; λ_{max} (EtOH) 387.5nm (ε_m 10,250), 324.5 (23,920); δ_H ($CDCl_3$ + d_4-MeOH) *inter alia* 0.90 (3H, d, *J* 7.1Hz, 17-H_3), 1.22 (3H, d, *J* 6.2Hz, 14-H_3), 3.32 (3H, s, NMe), 6.18 (1H, s, 2-H), 6.73 (1H, s, 3'''-H), 6.88 (2H, d, *J* 8.9Hz, 3', 5'-H_2), 7.81 (2H, d, *J* 8.8Hz, 2', 6'-H_2); *m/z* (Electrospray) 677 (*M*H$^+$, 100%). The ^{1}H spectrum indicated that the title compound was essentially in the enolic form.

Example 10 - 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-{4-[4-(1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylbut-1-yloxy)phenyl}but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran - Using the method described in Example 1f, the product from Example 1e (180mg, 0.345mmol) was reacted with holothin hydrochloride (99mg, 0.474mmol) to give the title compound (41mg, 17%); ν_{max} (KBr) 3404, 1636, 1599, 1506cm^{-1}; λ_{max} (EtOH) 387.5nm (ε_m 10,154) 323.5 (22,970); δ_H ($CDCl_3$/d_4-MeOH) *inter alia* 0.92 (3H, d, *J* 7.1Hz, 17-H_3), 1.21 (3H, d, *J* 6.3Hz, 14-H_3), 6.90 (1H, s, 3'''-H), 6.95 (2H, d, *J* 8.9Hz, 3', 5'-H_2), 7.84 (2H, d, *J* 8.9Hz, 2', 6'-H_2); *m/z* (Electrospray) 677 (*M*H$^+$, 100%). The 'H spectrum indicated that the title compound was essentially in the enolic form.

Example 11 - 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-{4-(3-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylprop-1-yloxy]phenyl}but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran - Using the method described in Example 1f, the product from Example 9e (577mg, 1.13mmol) was reacted with holothin hydrochloride (353mg, 1.69mmol) to give the title compound (206mg, 27%); ν_{max} (KBr) 3414, 1653, 1607cm^{-1}; λ_{max} (EtOH) 324.5nm (ε_m 22,566), 385. 5 (10,486); δ_H ($CDCl_3$/d_4-MeOH) *inter alia* 0.93 (3H, d, *J* 7.0Hz, 17-H_3), 1.21 (3H, d, *J* 6.3Hz, 14-H_3), 6.19 (~1H, s, 2-H), 6.85 (1H, s, 3'''-H), 6.94 (2H, d, *J* 8.8Hz, 3', 5'-H_2), 7.84 (2H, d, *J* 8.8Hz, 2', 6'-H_2); *m/z* (Electrospray) 663 (*M*H$^+$, 100%).

Example 12 - 2-{4-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylbutoxy}thiazol-5-yl 1-normon-2-yl ketone A

a) 2-{5,5,5-tris(Methylthio)pent-1-oxy}thiazole - 3,4-Dihydro-2H-pyran (9.3ml, 101.9mmol) was added to 4-bromobutanol (12.94g, 84.6mmol) in diethyl ether (160ml). After 2 hours at room temperature a further portion of 3,4-dihydro-2H-pyran (5.0ml, 59.9mmol) was added and the mixture stirred for 1 hour. Saturated

sodium hydrogen carbonate solution (100ml) was added and the mixture extracted with diethyl ether and dried ($MgSO_4$). Evaporation to dryness under reduced pressure and purification by column chromatography on silica gel, using 50% dichloromethane in hexane as eluent, gave 2-(4-bromobutoxy)tetra-hydropyran as a colourless oil (16.9g, 84%); δ_H ($CDCl_3$) 1.50-2.10 (10H, m, 5 x H_2), 3.40-3.92 (6H, m, 4'-H_2, 1'-H_2, 6-H_2), and 4.60 (1H, t, *J* 3.7Hz, 2-H).

n-Butyllithium (2.3M in hexane, 34.6ml, 79.7mmol) was added dropwise to tris(methylthio)methane (8.83ml, 66.3mmol) in dry tetrahydrofuran (120ml) at -78°C. After 1.5 hours the above compound (16.8g, 66.3mmol) in dry tetrahydrofuran (25ml) was added dropwise keeping the temperature below -60°C. The mixture was stirred at -60°C for 20 minutes, allowed to warm to -45°C and stirred for a further 2 hours. Saturated ammonium chloride solution (120ml) was added and extraction with diethyl ether, drying ($MgSO_4$) and evaporation to dryness under reduced pressure gave 5,5,5-tris(methylthio)-1-(tetrahydropyran-2-yl)oxypentane (22.6g, 102% crude); δ_H ($CDCl_3$) 1.50-2.00 (12H, m, 6 x H_2), 2.10 (9H, s, 3 x SCH_3), 3.38-3.94 (4H, m, 1-H_2, 6'-H_2), and 4.58 (1H, t, *J* 3.9Hz, 2'-H).

4-Toluene sulphonic acid (0.8g, 4 2mmol) was added to the above compound (13.1g, 42.2mmol) in methanol (200ml) and stirred for 1 hour at room temperature. Sodium hydrogen carbonate solution (100ml, saturated) was added and the mixture extracted with diethyl ether. Drying ($MgSO_4$), evaporation to dryness under reduced pressure and purification by chromatography on silica, using 10-40% ethyl acetate in hexane as eluent, gave 5,5,5-tris(methylthio)pentanol as a colourless oil (8.49g, 89%); δ_H ($CDCl_3$) 1.50-1.69 (7H, m, OH, 3 x H_2), 2.10 (9H, s, 3 x SCH_3), and 3.53 (2H, t, *J* 6.4Hz, 1-H_2).

Sodium hydride (60% dispersion in oil, 0.9g, 37.5mmol) was suspended in dry tetrahydrofuran (5ml) and stirred whilst the above compound (8.49g, 37.5mmol) in dry tetrahydrofuran (45ml) was added dropwise. After the addition the mixture was stirred for 2 hours. 2-Bromothiazole (6.76g, 41.2mmol) was added and the mixture heated to 40°C and stirred for 4 hours. The reaction mixture was diluted with water (100ml) and extracted with diethyl ether and dried ($MgSO_4$). Evaporation to dryness under reduced pressure and column chromatography on silica, using 5-15% ethyl acetate in hexane as eluent, gave the title compound (7.4g, 63%); δ_H ($CDCl_3$) 1.72-2.00 (6H, m, 3 x H_2), 2.10 (9H, s, 3 x SCH_3), 4.33 (2H, t, *J* 6.1Hz, 1'-H_2), 6.67 (1H, d, *J* 3.9Hz, 5-H), and 7.10 (1H, d, *J* 3.8Hz, 4-H).

b) **2-(5,5,5-*tris*(Methylthio)pent-1-oxy)thiazol-5-yl 1-(6,7,13-O-tristrimethylsilyl normon-2-yl) ketone A** - n-Butyllithium (1.5M in hexane, 1.81ml, 2.72mmol) was added dropwise with stirring to 2-(5,5,5-tris(methylthio)pent-1-oxy)thiazole (0.84g, 2.72mmol) in dry tetrahydrofuran (7ml) at -78°C. The mixture

was stirred for 1.5 hours and then N-methoxy-N-methyl-6,7,13-O-tris(trimethylsilyl)monamide A (WO93/06118, SmithKline Beecham p.l.c.) (1.643g, 2.72mmol) in dry tetrahydrofuran (4ml) was added dropwise. Stirred at -78°C for 1.5 hours, warmed to -30°C over 1 hour, then quenched with glacial acetic acid (0.245g, 4mmol) in diethyl ether (1ml). The mixture was warmed to 0°C diluted with water and extracted with diethyl ether. Drying ($MgSO_4$), evaporation to dryness under reduced pressure and purifying by column chromatography on silica, using 10% ethyl acetate in hexane as eluent, gave the title compound (1.17g, 50%); ν_{max} (KBr) 3370, 2963, 2916, 1648, 1480, 1455, 1253, and 1054cm^{-1}; λ_{max} (EtOH) 303nm (ε_m 21,221); δ_H ($CDCl_3$) (*inter alia*) 0.10-0.24 (27H, m, 9 x $SiCH_3$), 1.19 (3H, d, *J* 7.4Hz, 14-H_3), 2.01-2.20 (10H, m, 3 x SCH_3, 4-H), 2.58-2.72 (3H, m, 10, 11 and 4-H), 3.40 (1H, dd, *J* 2.4, 7.0Hz, 6-H), 3.56 (1H, d, *J* 11.4Hz, 16-H), 3.68-3.98 (4H, m, 5, 7, 13 and 16-H), 4.40-4.50 (2H, m, 1"-H_2), 6.55 (1H, s, 2-H), and 7.75 (1H, s, 4'-H).

c) **2-(5,5,5-*tris*(Methylthio)pent-1-oxy)thiazol-5-yl 1-normon-2-yl ketone A** - The above product (1.06g, 1.24mmol) was dissolved in tetrahydrofuran (25ml). Hydrochloric acid (6.2ml, 0.4M) was added and the solution stirred for two minutes. Saturated sodium hydrogen carbonate solution (20ml) was added and the mixture extracted with ethyl acetate. Drying ($MgSO_4$), evaporation to dryness under reduced pressure and purification by column chromatography on silica gel, using 0-5% methanol in dichloromethane as eluent, gave the title compound (0.71g, 90%); ν_{max} (KBr) 2963, 1648, 1480, 1455, 1349, and 1258cm^{-1}; λ_{max} (EtOH) 303nm (ε_m 21,221); δ_H ($CDCl_3$) (*inter alia*) 0.95 (3H, d, *J* 7.0Hz, 17-H_3), 1.22 (3H, d, *J* 6.1Hz, 14-H_3), 1.70-2.04 (9H, m, 3 x H_2, 9-H_2 and 8-H), 2.15 (9H, s, 3 x SCH_3), 2.24 (3H, s, 15-H_3), 4.45 (2H, t, 1"-H_2), 6.58 (1H, s, 2-H), and 7.75 (1H, s, 4'-H).

d) **2-(4-Methoxycarbonylbutoxy)thiazol-5-yl 1-normon-2-yl ketone A** - The title compound was prepared from the product of Example 12c (0.619g, 0.97mmol) by the method described in Example 2d. The product was a white foam (0.301g, 57%); ν_{max} (KBr) 2921, 1736, 1456, 1258, 1186, and 1059cm^{-1}; λ_{max} (EtOH) 301.5nm (ε_m 20,078); δ_H (CD_3OD) (*inter alia*) 0.95 (3H, d, *J* 7.0Hz, 17-H_3), 1.20 (3H, d, *J* 6.4Hz, 14-H_3), 1.70-2.08 (9H, m, 3 x H_2, 9-H_2 and 8-H), 2.25 (3H, s, 15-H_3), 3.70 (3H, s, CO_2CH_3), 4.50 (2H, t, *J* 5.9Hz, 1"-H_2), 6.23 (1H, s, 2-H), and 7.95 (1H, s, 4'-H); *m/z* 541 (M^+, 14%) and 115 (100). (Found: M^+, 541.2359. $C_{26}H_{39}HO_9S$ requires *M*, 541.2346).

e) **2-(4-Carboxybutoxy)thiazol-5-yl 1-normon-2-yl ketone A** - The title compound was prepared from the product of Example 12d (0.230g, 0.43mmol) using the method described in Example 8b. The product was a white gum (0.187g, 83%); δ_H (CD_3OD) (*inter alia*) 0.96 (3H, d, *J* 7.0Hz, 17-H_3), 1.21 (3H, d, *J* 6.4Hz, 14-H_3),

2.25 (3H, s, 15-H_3), 2.39 (2H, t, *J* 7.1Hz, 4"-H_2), 4.51 (2H, t, *J* 6.1Hz, 1"-H_2), 6.74 (1H, s, 2-H), and 7.94 (1H, s, 4'-H); *m/z* 527 (M^+, 0.5%), 128 (48), 100 (100), and 56 (94); *m/z* (NH_3, DCI) 528 (MH^+, 4%), 147 (100), and 91 (100).

f) 2-[4-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylbutoxy]-thiazol-5-yl 1-normon-2-yl ketone A - The title compound was prepared from the product of Example 12e (0.170g, 0.32mmol) using the method described in Example 7e. The product was an orange foam (0.151g, 68%); ν_{max} (KBr) 3415, 1669, 1648, 1600, 1480, and 1454cm^{-1}; λ_{max} (EtOH) 250 (ε_m 9,390), 304 (19,226) and 391nm (8,600); δ_H ($CDCl_3$/ CD_3OD) 0.94 (3H, d, *J* 7.1Hz, 17-H_3), 1.22 (3H, d, *J* 6.3Hz, 14-H_3), 1.34-1.44 (1H, m, 12-H), 1.65-2.06 (7H, m, 8-H, 9-H_2, 2"-H_2, 3"-H_2), 2.24 (3H, s, 15-H_3), 2.33 (1H, dd, *J* 9.3, 14.7Hz, 4-H), 2.46 (2H, t, *J* 7.0Hz, 4"-H_2), 2.68-2.85 (3H, m, 4, 10, 11-H), 3.35 (3H, s, NCH_3), 3.41 (1H, dd, *J* 3.1, 9.1Hz, 6-H), 3.58 (1H, br.d, *J* 11.3Hz, 16-H), 3.69-3.96 (4H, m, 5,7,13,16-H), 4.47 (2H, t, *J* 5.9Hz, 1"-H_2), 6.60 (1H, s, 2-H), 6.81 (1H, s, 3'"-H), and 7.77 (1H, s, 4'-H); δ_C ($CDCl_3$/CD_3OD) 12.4 (C-17), 20.2 (C-15), 20.4 (C-14), 21.8 (C-3"), 27.9 (NCH_3), 28.3 (C-2"), 31.9 (C-9), 35.4 (C-4"), 39.9 (C-8), 42.3 (C-12), 43.5 (C-4), 55.8 (C-10), 61.0 (C-11), 65.7 (C-16), 68.7 (C-6), 70.3 (C-7), 70.7 (C-13), 72.3 (C-1"), 75.1 (C-5), 110.6 (C-3'"), 114.5 (C-6a'"), 120.9 (C-2), 134.0, 135.7 and 136.7 (C-5', 3a'", 6'"), 142.5 (C-4'), 158.2 (C-3), 167.4 (C-5'"), 171.6 (C-5"), 179.3 (C-2'), and 183.4 (C-1); *m/z* (Electrospray) 696.3 (MH^+, 100%).

Example 13 - 2-{1,2-Dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl}carbamoylmethyloxythiazol-5-yl 1-normon-2-yl ketone A

a) 2,2,2-*tris*(Methylthio)ethanol - n-Butyllithium (2.5M in hexane, 6.38ml, 16.0mmol) was added dropwise to tris(methylthio)methane (2.05g, 13.28mmol) in dry tetrahydrofuran (40ml) at -78°C. Stirred for 1.5 hours. Paraformaldehyde (3g) was heated in a flask and the formaldehyde generated was blown over the surface of the vigorously stirred reaction mixture with a stream of argon. Stirred at -50°C for a further 1.5 hours, then saturated ammonium chloride solution (50ml) was added. The mixture was extracted with diethyl ether, dried ($MgSO_4$), evaporated to dryness under reduced pressure and purified by chromatography on silica, using 33% ethyl acetate in hexane as eluent, to give the title compound as a colourless oil (1.7g, 72%); δ_H ($CDCl_3$) 2.13 (9H, s, 3 x SCH_3), 2.52 (1H, t, *J* 6.6Hz, OH), and 3.72 (2H, d, *J* 6.6Hz, CH_2). Addition of D_2O gave 2.13 (9H, s, 3 x SCH_3) and 3.72 (2H, s, CH_2).

b) 2-(2,2,2-*tris*(Methylthio)ethoxy)thiazole - Sodium hydride (60% suspension in oil, 0.382g, 9.55mmol) was stirred in dry tetrahydrofuran (5ml) and a solution of the above compound (1.76g, 9.55mmol) in dry tetrahydrofuran (10ml) was added over 15 minutes. The reaction was stirred for a further 1.5 hours. Bromothiazole

(0.947ml, 10.5mmol) was then added over 15 minutes, the mixture warmed to 40°C and stirred for 4 hours, then at ambient temperature overnight. Water (50ml) was added. Extraction with diethyl ether, drying ($MgSO_4$), evaporation and chromatography on silica, using 66% dichloromethane in hexane as eluent, gave the crude title compound (contained 25% bromothiazole as seen by n.m.r.) (2.0g, 78%); δ_H ($CDCl_3$) 2.22 (9H, s, 3 x SCH_3), 4.81 (2H, s, 1'-H_2), 6.71 (1H, d, *J* 3.9Hz, 5-H), and 7.11 (1H, d, *J* 3.9Hz, 4-H).

c) **2-{2,2,2-*tris*(Methylthio)ethoxy}thiazol-5-yl 1-(6,7,13-O-tristrimethylsilyl normon-2-yl) ketone A** - n-Butyllithium (2.4M in hexane, 4.4ml, 10.6mmol) was added dropwise with stirring to a solution of the above compound (crude containing 25% bromothiazole, 2.0g, 7.5mmol) in dry tetrahydrofuran (7ml) at -70°C over 15 mins. The mixture was stirred at -70°C for 1.5 hours. A solution of N-methoxy-N-methyl-6,7,13-O-tris(trimethylsilyl)monamide A (WO93/06118, SmithKline Beecham plc). (5.0g, 8.28mmol) in dry tetrahydrofuran (10ml) was added over 10 minutes and the mixture stirred at -70C for 1.5 hours. The mixture was allowed to warm to -30°C over 30 min. and stirred at this temperature for 1 hour. The reaction was then quenched with glacial acetic acid (0.746mg in diethyl ether [2ml]), warmed to 0°C, diluted with water (20ml) and extracted with diethyl ether. Drying ($MgSO_4$), evaporation to dryness under reduced pressure and chromatography on silica, using 8-16% ethyl acetate in hexane as eluent, gave the title compound as a colourless oil (1.49g, 29%); δ_H ($CDCl_3$) (*inter alia*) 0.11-0.29 (27H, m, 9 x $SiCH_3$), 0.95 (3H, d, *J* 7.0Hz, 17-H_3), 1.20 (3H, d, *J* 6.4Hz, 14-H_3), 2.21 (9H, s, 3 x SCH_3), 3.41 (1H, dd, *J* 2.4, 8.9Hz, 6-H), 3.56 (1H, d, *J* 11.3Hz, 16-H), 3.80-4.00 (4H, m, 5,7,13 and 16-H), 4.35 (2H, s, 1"-H_2), 6.55 (1H, s, 2-H), and 7.72 (1H, s, 4'-H).

d) **2-{2,2,2-*tris*(Methylthio)ethoxy}thiazol-5-yl 1-normon-2-yl ketone A** - The above product (1.35g, 1.67mmol) was dissolved in tetrahydrofuran (33ml). Hydrochloric acid (8.34ml, 0.4M) was added and the mixture stirred for 2 minutes. Saturated sodium hydrogen carbonate solution (17ml) was added and the mixture extracted with ethyl acetate. Drying ($MgSO_4$), evaporation to dryness under reduced pressure and purification by column chromatography on silica, using 5% methanol in dichloromethane as eluent, gave the title compound as a yellow foam (0.62g, 62%); δ_H ($CDCl_3$) (*inter alia*) 0.95 (3H, d, *J* 7.0Hz, 17-H_3), 1.12 (3H, d, *J* 6.3Hz, 14-H_3), 2.22 (9H, s, 3 x SCH_3), 2.29 (3H, s, 15-H_3), 3.61 (1H, d, *J* 10.0Hz, 16-H), 4.35 (2H, s, 1"-H_2), 6.60 (1H, s, 2-H), and 7.75 (1H, s, 4'-H).

e) **2-(4-Methoxycarbonylmethyloxy)thiazol-5-yl 1-normon-2-yl ketone A** - The above compound (0.88g, 1.48mmol) was dissolved in methanol (60ml) and cooled to -40°C. Mercuric oxide (yellow, 0.321g, 1.48mmol) and mercuric chloride (1.20g, 4.42mmol) were added and the mixture stirred for 50 minutes. The mixture

was filtered through kieselguhr into cold saturated ammonium chloride solution (150ml) and washed with methanol (20ml). The mixture was extracted with dichloromethane. Drying ($MgSO_4$), evaporation to dryness and chromatography on silica gel, using 10% methanol in ethyl acetate as eluent, gave a mixture of the desired product and the ortho ester in approx. 1:1 proportions (0.104g, 13%). This was dissolved in methanol (28ml) and water (28ml) and 0.4M HCl (1.9ml) added. After 2 minutes, saturated sodium hydrogen carbonate solution (4ml) was added. This converted the ortho ester to the desired product. The mixture was extracted with dichloromethane, and the extracts washed with brine, dried and evaporated. Chromatography on silica gel, using 0-6% methanol in diethyl ether as eluent, gave the desired product as a white foam (0.062g, 8.4%); ν_{max} (KBr) 2923, 1762, 1646, 1422, 1184, and 1049cm^{-1}; λ_{max} (EtOH) 299 (ε_m 19,323); δ_H (CD_3OD) (*inter alia*) 0.95 (3H, d, *J* 7.1Hz, 17-H_3), 1.20 (3H, d, *J* 6.4Hz, 14-H_3), 2.22 (3H, s, 15-H_3), 3.40 (1H, dd, *J* 2.1, 9.0Hz, 6-H), 3.80 (3H, s, CO_2CH_3), 5.10 (2H, s, 1"-H_2), 6.71 (1H, s, 2-H), and 7.90 (1H, s, 4'-H).

f) **2-(Carboxymethyloxy)thiazol-5-yl 1-normon-2-yl ketone A** - Protease subtilisin Carlsberg (157mg) was added to a solution of the above product (290mg, 0.58mmol) in acetone (30ml) and disodiumhydrogen phosphate buffer (0.1M, 270 ml, pH 7) and the mixture stirred for 2.5 hours. The solution was reduced in volume (100ml) at low pressure and washed with ethyl acetate (30ml). The solution was then layered with ethyl acetate (40ml) saturated with solid sodium chloride and the pH adjusted to 3.5 using phosphoric acid (1.5M). The mixture was separated and the aqueous phase re-extracted with ethyl acetate (2 x 40ml). The organic phase was washed with brine, dried ($MgSO_4$) and evaporated to dryness to give the title compound as a colourless oil (185mg, 65%); δ_H (CD_3OD) (*inter alia*) 0.96 (3H, d, *J* 7.0Hz, 17-H_3), 1.21 (3H, d, *J* 6.3Hz, 14-H_3), 2.25 (3H, s, 15-H_3), 2.71 (1H, dd, *J* 2.3, 7.4Hz, 11-H), 3.41 (1H, dd, *J* 3.0, 9.0Hz, 6-H), 3.61 (1H, d, *J* 11.2Hz, 16-H), 3.82-3.98 (4H, m, 5,7,13 and 16-H), 5.05 (2H, s, 1"-H_2), 6.72 (1H, s, 2-H), and 7.92 (1H, s, 4'-H).

g) **2-{1,2-Dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl}carbamoylmethyloxythiazol-5-yl 1 normon-2-yl ketone A** - The product from Example 13f (162mg, 0.335mmol) in dry tetrahydrofuran (31ml) under argon at 0°C was treated sequentially with triethylamine (49.9ul, 0.359mmol) and isobutylchloroformate (46.6ul, 0.359mmol). After stirring for 30 minutes the mixture was treated with triethylamine (66ul, 0.478mmol) followed by 6-amino-1,2-dithiolo-[4,3-b]-pyrrol-5(4H)-one hydrochloride (90mg, 0.43mmol) and the mixture stirred for 18 hours after allowing to attain ambient temperature. The mixture was diluted with dichloromethane, washed with water and brine, dried ($MgSO_4$) and evaporated to dryness under

reduced pressure. The product was purified by column chromatography on silica gel, using 1% methanol in methyl acetate as eluent, to give the title compound as a bright orange solid (46mg, 21%); ν_{max} (KBr) 2942, 1682, 1651, 1640, 1464, and 1261cm^{-1}; λ_{max} (EtOH) 299 (ε_m 13,405) and 391nm (7,312); δ_H (CD_3OD) (*inter alia*) 0.95 (3H, d, *J* 6.9Hz, 17-H_3), 1.21 (3H, d, *J* 6.4Hz, 14-H_3), 2.25 (3H, s, 15-H_3), 2.35 (1H, dd, *J* 9.4, 14.3Hz, 4-H), 2.70-2.78 (2H, m, 4-H and 11-H), 3.41 (1H, dd, *J* 3.1, 9.0Hz, 6-H), 3.60 (1H, d, *J* 11.5Hz, 16-H), 3.75-3.84 (2H, m, 13-H and 5-H), 3.86-3.92 (2H, m, 16-H and 7-H), 5.15 (2H, s, 1"-H_2), 6.74 (1H, s, 2-H), 7.13 (1H, s, 3'"-H), and 7.94 (1H, s, 4'-H); *m/z* (ESI) 640 (M^+, 1%), 527 (85), and 258 (100).

Example 14 - N-{8-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]-2-oxooct-1-yl}monamide A

a) **Methyl 9-bromo-8-oxononanoate** - Suberic acid monomethyl ester (2.50g, 13.3mmol) was dissolved in dichloromethane (30ml) and dimethylformamide (0.1ml), and treated dropwise with oxalyl chloride (1.28ml, 14.6mmol) in dichloromethane (5ml). The reaction was stirred under argon for 30 minutes, then evaporated to dryness, and again from toluene.

Diazomethane (*ca.* 30mmol) was then generated slowly, by the method of Lombardi (Chem. & Ind., *21*, 108 (1990)), and bubbled into a cooled solution of the acid chloride in diethyl ether (150ml). The mixture was stirred for a further 30 minutes, then concentrated hydrobromic acid (10ml) was added slowly. After 30 minutes of vigorous stirring the phases were separated, and the acidic aqueous phase extracted with ether (2 x 50ml). The combined ethereal phases were washed with saturated sodium hydrogen carbonate (x2) and brine, dried and evaporated to give a white oily solid (1.60g, 45%), which was used without further purification; ν_{max} (CH_2Cl_2) 2945, 1730 and 1175cm^{-1}; δ_H ($CDCl_3$) 1.24-1.49 (4H, m, 2 x H_2), 1.51-1.79 (4H, m, 2 x H_2), 2.31 (2H, t, *J* 7.4Hz, 2-H_2), 2.66 (2H, t, *J* 7.3Hz, 7-H_2), 3.67 (3H, s, CO_2CH_3), and 3.88 (2H, s, 9-H_2); *m/z* 265/267 (MH^+, 1%), 233/235 (*M*-OMe, 20), 171 (94), 139 (91) and 129 (100); *m/z* (NH_3, DCI) 282/284 (MNH_4^+, 90%), 204 (100), and 187 (99). (Found: M^+-OMe, 233.0180. $C_9H_{14}BrO_2$ requires *M*-OMe, 233.0177).

b) **Methyl 9-azido-8-oxononanoate** - Methyl 9-bromo-8-oxononanoate (1.57g, 5.92mmol) was dissolved in acetone (30ml) and water (10ml), then sodium azide (0.423g, 6.5mmol) was added, and the mixture stirred for 18 hours. The solution was reduced in volume *in vacuo* and extracted with ethyl acetate (x2). The combined organic extracts were washed with brine, dried and evaporated to give a colourless oil (1.28g). This was purified by column chromatography on silica (36g), eluting with

10-15% ethyl acetate in hexane, to give the title compound as a colourless oil (1.10g, 82%), which solidified on refrigeration; ν_{max} (CH_2Cl_2) 2940, 2109, and 1730cm^{-1}; δ_H ($CDCl_3$) 1.23-1.48 (4H, m, 2 x H_2), 1.52-1.78 (4H, m, 2 x H_2), 2.30 (2H, t, *J* 7.4Hz, 2-H_2), 2.44 (2H, t, *J* 7.3Hz, 7-H_2), 3.66 (3H, s, CO_2CH_3), and 3.93 (2H, s, 9-H_2); *m/z* (NH_3, DCI) 245 (MNH_4^+, 100%), 228 (MH^+, 17), 204 (64), 188 (71), and 187 (83).

c) **Aminomethyl 6-methoxycarbonylhex-1-yl ketone hydrochloride** - Methyl 9-azido-8-oxononanoate (1.08g, 4.75mmol) was dissolved in methanol (15ml), water (5ml) and 5N hydrochloric acid (2.5ml), and the mixture hydrogenated over 10% palladium on carbon (0.1g) for 1 hour. The mixture was filtered through kieselguhr, washing with water, and evaporated to dryness to give an off-white solid. This was then triturated with diethyl ether and dried *in vacuo* to give a white powder (0.983g, 87%); ν_{max} (KBr) 3428, 2938, 1721, and 1694cm^{-1}; δ_H (d_6-DMSO) showed the product to be a mixture (*ca.* 1:1) of the methyl ester and corresponding acid, as shown by two triplets at 2.19 and 2.29.

d) **N-(8-Methoxycarbonyl-2-oxooct-1-yl)monamide A** - Monic acid A (1.376g, 4.0mmol) was dissolved in dry tetrahydrofuran (40ml) and triethylamine (0.61ml, 4.4mmol), cooled in an ice bath, and treated with isobutyl chloroformate (0.52ml, 4.0mmol). The mixture was stirred for ½ hour, then triethylamine (1.22ml, 8.8mmol) was added, followed by a solution of the product of Example 14c (0.96g, *ca.* 4mmol) in tetrahydrofuran:water (1:1, 10ml). The reaction was stirred for 2½ hours while warming to room temperature, then diluted with ethyl acetate and washed with sodium hydrogen carbonate solution and brine, dried and evaporated to give a pale yellow oil (1.27g). The aqueous phases were saturated with sodium chloride, layered with ethyl acetate, and adjusted to pH 3.2 with 1.5M phosphoric acid. The layers were separated and the aqueous extracted with ethyl acetate. The combined organic extracts (from pH 3.2) were washed with brine, dried and evaporated to give a second product (0.80g, *ca.* 39%).

The second product was shown by n.m.r. to be a mixture (*ca.* 2:1) of N-(8-carboxy-2-oxooct-1-yl)monamide A and monic acid A.

The first product was purified by column chromatography on silica (35g), eluting with 0-5% methanol in dichloromethane, to give the title compound as a colourless gum (0.715g, 34%); δ_H (CD_3OD) (*inter alia*) 0.95 (3H, d, *J* 7.1Hz, 17-H_3), 1.20 (3H, d, *J* 6.4Hz, 14-H_3), 2.14 (3H, s, 15-H_3), 2.31 (2H, t, *J* 7.4Hz, 8'-H_2), 2.48 (2H, t, *J* 7.3Hz, 3'-H_2), 3.64 (3H, s, CO_2CH_3), 4.02 (2H, s, 1'-H_2), and 5.82 (1H, s, 2-H); *m/z* 527 (M^+, 1%), 509 (1), 283 (34), 111 (78), and 55 (100). (Found: M^+, 527.3081. $C_{27}H_{45}NO_9$ requires *M*, 527.3094).

e) **N-{8-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]-2-**

oxooct-1-yl}monamide A - Impure N-(8-carboxy-2-oxooct-1-yl)monamide A (0.39, *ca.* 0.88mmol) was dissolved in dry tetrahydrofuran (40ml) and triethylamine (0.14ml, 0.97mmol), cooled in an ice/salt bath and treated with isobutyl chloroformate (0.12ml, 0.88mmol). The reaction was stirred for 1 hour, then triethylamine (0.16ml, 1.15mmol) and 6-amino-4-methyl-1,2-dithiolo-[4,3-b]-pyrrol-5(4H)-one hydrochloride (0.236g, 1.06mmol) were added, and stirring continued for a further 21 hours. The mixture was diluted with ethyl acetate, washed with saturated sodium hydrogen carbonate solution, and brine, dried and evaporated. The residue was purified by column chromatography on silica (22g), eluting with 0-6% methanol in dichloromethane, to give the title compound as an orange foam (0.206g, 60%); ν_{max} (KBr) 3419, 2926, 1733, 1668, 1637, and 1526cm^{-1}; λ_{max} (EtOH) 214 (ε_m 24,029), 315 (2,986), and 389nm (8,379); δ_H (CD_3OD) 0.94 (3H, d, *J* 7.1Hz, 17-H_3), 1.20 (3H, d, *J* 6.4Hz, 14-H_3), 1.30-1.48 (5H, m, 12-H, 5'-H_2, 6'-H_2), 1.52-1.77 (6H, m, 9-H_2, 4'-H_2, 7'-H_2), 1.90-2.02 (1H, m, 8-H), 2.13 (3H, d, *J* 0.7Hz, 15-H_3), 2.10-2.25 (1H, m, 4-H), 2.38 (2H, t, *J* 7.4Hz, 8'-H_2), 2.49 (2H, t, *J* 7.3Hz, 3'-H_2), 2.61 (1H, br.d, *J* 14.2Hz, 4-H), 2.70 (1H, dd, *J* 2.2, 7.6Hz, 11-H), 2.80 (1H, dt, *J* 2.2, 5.7Hz, 10-H), 3.35 (3H, s, NCH_3), 3.31-3.39 (1H, m, 6-H), 3.55 (1H, br.d, *J* 11.6Hz, 16-H), 3.68-3.92 (4H, m, 5,7,13, 16-H), 4.02 (2H, s, 1'-H_2), 5.83 (1H, s, 2-H), and 7.25 (1H, s, 3"-H); δ_C (CD_3OD) 12.1 (C-17), 19.0 (C-15), 20.3 (C-14), 24.4 (C-7'), 26.5 (C-5'), 28.1 (NCH_3), 29.8 (C-6'), 29.9 (C-4'), 33.0 (C-9), 36.5 (C-8'), 40.4 (C-3'), 41.7 (C-8), 43.8 (C-4 and C-12), 49.7 (C-1'), 56.9 (C-10), 61.3 (C-11), 66.3 (C-16), 70.1 (C-6), 70.7 (C-7), 71.6 (C-13), 76.3 (C-5), 112.8 (C-3"), 115.4 (C-6a"), 120.6 (C-2), 135.9 (C-3a"), 137.6 (C-6"), 153.2 (C-3), 168.6 (C-1), 169.7 (C-5"), 174.2 (C-9'), and 208.4 (C-2'); *m/z* (Electrospray) 704 (*M*Na^+, 1%), 699 (*M*NH_4^+, 2), 682 (*M*H^+, 2.5), 437 (2), and 147 (100).

Example 15 - 5-[6-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylhexyl]-2-(1-normon-2-yl)oxazole A

N-{8-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]-2-oxooct-1-yl}monamide A (0.160g, 0.235mmol) (example 14) was suspended in dry dichloromethane (20ml) and pyridine (0.23ml, 2.82mmol), cooled in an ice bath and treated sequentially with trichloroacetyl chloride (0.23ml, 1.88mmol) and 4-dimethylaminopyridine (few crystals). The mixture was stirred for 1½ hours, reduced in volume *in vacuo*, and diluted with ethyl acetate. This solution was washed with water, 5% aqueous citric acid, saturated sodium hydrogen carbonate solution, and brine, dried and evaporated.

The residue was dissolved in methanol (5ml), and potassium carbonate (0.138g, 1.0mmol) added. The mixture was stirred for 1 hour, diluted with water and

extracted with ethyl acetate (x3). The combined organic extracts were washed with brine, dried and evaporated. The crude product was purified by column chromatography on silica (8g), eluting with 0-5½% methanol in dichloromethane, to give the title compound as an orange foam (0.040g, 26%); λ_{max} 266 and 390nm; δ_H (CD_3OD) 0.96 (3H, d, *J* 7.1Hz, 17H_3), 1.21 (3H, t, *J* 6.5Hz, 14-H_3), 1.31-1.54 (5H, m, 12-H, 3"-H_2, 4"-H_2), 1.59-1.79 (6H, m, 9-H_2, 2"-H_2, 5"-H_2), 1.91-2.03 (1H, m, 8-H), 2.19 (3H, s, 15-H_3, 2.28 (1H, dd, *J* 9.6, 14.4Hz, 4-H), 2.40 (2H, t, *J* 7.3Hz, 6"-H_2), 2.66-2.87 (5H, m, 4, 10, 11-H, 1"-H_2), 3.37 (3H, s, NCH_3), 3.38-3.46 (1H, m, 6-H), 3.56 (1H, br.d, *J* 11.5Hz, 16-H), 3.73-3.95 (4H, m, 5,7,13,16-H), 6.14 (1H, s, 2-H), 6.80 (1H, s, 4'-H), and 7.23 (1H, s, 3'"-H); *m/z* (Electrospray) 686 (*M*Na^+, 5%), 664 (*M*H^+, 41), and 164 (100).

Example 16 - 5-[6-(1,2-Dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylhexyl]-2-(1-normon-2-yl)oxazole A

a) **5-(6-Methoxycarbonylhexyl)-2-(1-normon-2-yl)oxazole A** - Using the method described in Example 15, N-(8-methoxycarbonyl-2-oxooct-1-yl)monamide A (from Example 14d, 0.695g, 1.32mmol) was cyclised to give the title compound as a colourless gum (0.106g, 16%); δ_H (CD_3OD) (*inter alia*) 0.96 (3H, d, *J* 7.1Hz, 17-H_3), 1.21 (3H, d, *J* 6.4Hz, 14-H_3), 2.20 (3H, s, 15-H_3), 2.34 (2H, t, *J* 7.3Hz, 6"-H_2), 2.62-2.89 (5H, m, 4,10,11-H, 1"-H_2), 3.66 (3H, s, CO_2CH_3), 6.14 (1H, s, 2-H), and 6.80 (1H, s, 4'-H); *m/z* (DCI, NH_3) 510 (*M*H^+, 100%) and 265 (68).

b) **5-(6-Carboxyhexyl)-2-(1-normon-2-yl)oxazole A** - Using the method described in Example 8b, the product of the above reaction (0.097g, 0.19mmol) was reacted to give the title compound as a colourless gum (0.079g, 84%); δ_H (CD_3OD) (*inter alia*) 0.94 (3H, d, *J* 7.1Hz, 17-H_3), 1.20 (3H, d, *J* 6.5Hz, 15-H_3), 2.18 (3H, s, 15-H_3), 2.23-2.35 (3H, m, 4-H, 6"-H_2), 2.64-2.85 (5H, m, 4,10,11-H, 1"-H_2), 6.13 (1H, s, 2-H), and 6.79 (1H, s, 4'-H).

c) **5-[6-(1,2-Dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylhexyl]-2-(1-normon-2-yl)oxazole A** - Using the method described in Example 10, the product of the above reaction (0.075g, 0.151mmol) was reacted to give the title compound as an orange foam (0.046g, 47%); ν_{max} (KBr) 3416, 2925, 1640, 1597, and 1533cm^{-1}; λ_{max} (EtOH) 265 (ε_m 20,899) and 388nm (10,915); δ_H (CD_3OD) 0.94 (3H, d, *J* 7.2Hz, 17-H_3), 1.19 (3H, d, *J* 6.5Hz, 14-H_3), 1.32-1.49 (5H, m, 12-H, 3"-H_2, 4"-H_2), 1.58-1.78 (6H, m, 9-H_2, 2"-H_2, 5"-H_2), 1.89-2.01 (1H, m, 8-H), 2.17 (3H, s, 15-H_3), 2.27 (1H, dd, *J* 9.7, 14.5Hz, 4-H), 2.39 (2H, t, *J* 7.4Hz, 6"-H_2), 2.63-2.84 (5H, m, 4,10,11-H, 1"-H_2), 3.38 (1H, dd, *J* 3.1, 8.8Hz, 6-H), 3.56 (1H, br.d, *J* 11.5Hz, 16-H), 3.71-3.92 (4H, m, 5,7,13,16-H), 6.12 (1H, s, 2-H), 6.78 (1H, s, 4'-H), and 7.07 (1H, s, 3'"-H); *m/z* (Electrospray) 673 (*M*Na^+, 10%) and 650 (*M*H^+, 100).

Example 17 - 5-[4-(1,2-Dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylmethyloxyphenyl]-2-(1-normon-2-yl)oxazole A - Using the method described in Example 10, the product of Example 8b (0.212g, 0.41mmol) was reacted to give the title compound as an orange foam (0.104g, 38%); ν_{max} (KBr) 3385, 1666, 1537, 1498, and 1245cm^{-1}; λ_{max} (EtOH) 306 (ε_m 29,743) and 388nm (12,364); δ_H ($(CD_3)_2SO$) 0.83 (3H, d, *J* 7.0Hz, 17-H_3), 1.06 (3H, d, *J* 6.4Hz, 14-H_3), 1.25-1.41 (1H, m, 12-H), 1.54-1.69 (2H, m, 9-H_2), 1.77-1.89 (1H, m, 8-H), 2.17-2.31 (4H, m + s, 4-H, 15-H_3), 2.61-2.78 (3H, m, 4,10,11-H), 3.18-3.29 (1H, m, 6-H), 3.44 (1H, br.d, *J* 10.5Hz, 16-H), 3.59-3.78 (4H, m, 5,7,13,16-H), 4.50 (1H, d, *J* 4.7Hz, OH), 4.65 (1H, d, *J* 7.3Hz, OH), 4.76 (1H, d, *J* 3.5Hz, OH), 4.83 (2H, s, 1"-H_2), 6.18 (1H, s, 2-H), 7.04 (2H, d, *J* 9.2Hz, 2 x Ar-H), 7.14 (1H, s, 4'-H), 7.57 (1H, s, 3"'-H), 7.66 (2H, d, *J* 8.8Hz, 2 x Ar-H), 10.04 (1H, s, NH), and 10.83 (1H, s, NH); *m/z* (Electrospray) 672 (MH^+, 6%) and 296 (100).

Example 18 - N-{4-[3-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-ylaminocarbonyl)-propyloxy]phenyl}monamide A

a) N-(4-Hydroxyphenyl)monamide - The mixed anhydride of monic acid A (688mg, 2mmol) was treated with 4-hydroxyaniline as described in Example 5a to give the title compound (641mg, 74%); ν_{max} (KBr) 3400 (br), 1663, 1637 and 1513cm^{-1}; δ_H (250MHz, CD_3OD, Me_4Si), 0.95 (3H, d, *J* 7Hz, 17-H_3), 1.20 (3H, d, *J* 6.5Hz, 14-H_3), 1.40 (1H, m, 12-H), 1.69 (2H, m, 9-H_2), 1.97 (1H, m, 8-H), 2.20 (4H, m, 15-H_3, 4-H), 2.62-2.88 (3H, m, 10-H, 11-H, 4-H), 3.33-3.95 (6H, m, 5-H, 6-H, 7-H, 13-H, 16-H), 5.89 (1H, s, 2-H), 6.73 and 7.35 (4H, ABq, *J* 6.8Hz, Ph); *m/z* (EI^+) 435 (M^+, 12%).

b) N-[4-(3-Carboxypropyloxy)phenyl]monamide A - A solution of the product from Example 18a (218mg, 0.5mmol) and tetramethyl-guanidine (0.13ml, 1mmol) in dry DMF (5ml) under argon at room temperature was treated with (3,4,5,6-tetrahydropyran-2-yl) 4-bromobutanoate (251g, 1mmol). Stirred overnight, diluted with ethyl acetate, washed with saturated sodium hydrogen carbonate, brine, dried ($MgSO_4$) and evaporated. The crude product was separated by flash chromatography on silica eluting with mixtures of methanol in dichloromethane (130mg, 43%). The tetrahydropyranyl ester (382mg) in methanol (10ml) and water (5ml) at room temperature was treated with glacial acetic acid (2 drops). After 3 hours the mixture was evaporated, and flash chromatographed on silica eluting with mixtures of methanol in dichloromethane to give the title compound (291mg, 88%); ν_{max} (KBr) 3416 (br), 2924, 1715, 1665, 1636 and 1510cm^{-1}; δ_H (250MHz, CD_3OD, Me_4Si) 0.96 (3H, d, *J* 7Hz, 17-H_3), 1.21 (3H, d, *J* 6.4Hz, 14-H_3), 1.41 (1H, m, 12-H), 1.71

(2H, m, 9-H_2), 1.98 (1H, m, 8-H), 2.06 (2H, m, CH_2), 2.22 (4H, m, 4-H, 15-H_3), 2.45 (2H, t, *J* 7.3Hz, CH_2CO), 2.60-2.80 (3H, m, 4-H, 10-H, 11-H), 3.35-4.00 (6H, m, 5-H, 6-H, 7-H, 13-H, 16-H_2), 4.00 (2H, t, *J* 6.7Hz, OCH_2), 5.92 (1H, s, 2H), 6.88 and 7.46 (4H, ABq, *J* 9Hz, Ph); *m/z* (NH_3 DCI$^+$) 522 (*M*H$^+$, 29%).

c) **N-{4-[3-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl-aminocarbonyl)propyloxy]phenyl}monamide A** - The product from Example 18b (261mg) was converted to the title compound (106mg, 31%) by the method described in Example 5b. ν_{max} (KBr) 3418 (br), 2924, 1648, 1509, and 1230cm^{-1}; λ_{max} (EtOH) 393 (ε_m 10,298), 280.5 (ε_m 17,164); δ (250MHz, CD_3OD, Me_4Si) 0.96 (3H, d, *J* 7Hz, 17-H_3), 1.21 (3H, d, *J* 6.4Hz, 14-H_3), 1.41 (1H, m, 12-H), 1.70 (2H, m, 9-H_2), 1.98 (1H, m, 8-H), 2.05-2.30 (6H, m, 4-H, 15-H_3, CH_2), 2.60 (2H, t, *J* 7.3Hz, CH_2CO), 2.61-2.89 (3H, m, 4-H, 10-H, 11-H), 3.35 (3H, s, NMe), 3.35-3.95 (6H, m, 5-H, 6-H, 7-H, 13-H, 16-H_2), 4.03 (2H, t, *J* 6Hz, OCH_2), 5.91 (1H, s, 2-H), 6.88 and 7.44 (4H, ABq, *J* 9Hz, Ph), 7.25 (1H, s, 3"-H); δ_C (CD_3OD) 13.55 (C-17), 17.15 (C-15), 18.49 (C-14), 24.51 (C-3'), 26.17 (C-NCH_3), 31.16, 31.42 (C-9, C-2'), 39.86 (C-8), 41.70 (C-12), 42.13 (C-4), 55.06 (C-10), 59.43 (C-11), 64.50 (C-16), 66.58 (C-4'), 68.26 (C-7), 68.89 (C-6), 69.61 (C-13), 74.41 (C-5), 110.96 (C-3"), 113.61 (C-6a"), 113.63 and 121.06 (C-Ph), 119.64 (C-2), 131.33 (C-3a"), 135.26 (C-6"), 151.96 (C-5"), 165.66, 166.24 (C-1, C-3), 171.67 (C-1'); *m/z* (NH_3DCI^+) 690 (*M*H$^+$, 8%).

Example 19 - N-{4-[4-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-ylaminocarbonyl)-butyloxy]benzyl}monamide A

a) **Methyl 5-(4-methylphenoxy)pentanoate** - A mixture of 4-methylphenol (2.66g), tetramethylguanidine (3.4ml) and methyl 5-bromopentanoate (3.5ml) in dry DMF (20ml) was stirred at room temperature for 7 days. Diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$) and evaporated. The title compound (1.6g, 29%) was isolated by flash chromatography eluting with mixtures of ethyl acetate in hexane. δ_H (250MHz, $CDCl_3$, Me_4Si), 1.82 (4H, m, 2 x CH_2), 2.30 (3H, s, CH_3), 2.42 (2H, m, CH_2CO), 3.75 (3H, s, OCH_3), 3.98 (2H, m, OCH_2), 6.79 and 7.08 (4H, ABq, *J* 8.4Hz, Ar).

b) **Methyl 5-(4-azidomethylphenoxy)pentanoate** - A mixture of the product from Example 19a (1.6g) and N-bromosuccinimide (1.28g) in carbon tetrachloride (20ml) was refluxed under strong illumination for 30 minutes, cooled in an ice bath, filtered and evaporated. The unpurified bromide was redissolved in DMF (50ml) at 0°C and treated with sodium azide (0.47g). After 45 minutes the mixture was diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was flash chromatographed on silica eluting with mixture of ethyl acetate and

hexane to give the title compound (1.5g, 79%). ν_{max} (CH_2Cl_2) 2952, 2089, 1732 and 1248cm^{-1}; δ_H (250MHz, $CDCl_3$, Me_4Si) 1.85 (4H, m, 2 x CH_2), 2.43 (2H, m, CH_2CO), 3.68 (3H, s, OCH_3), 3.97 (2H, m, OCH_2), 4.26 (2H, s, CH_2N_3), 6.90-7.24 (4H, m, Ar); *m/z* (EI$^+$) 263 (*M*$^+$, 13%).

c) **Methyl 5-(4-aminomethylphenoxy)pentanoate** - The product from Example 19b (526mg) in ethanol (30ml) was hydrogenated at room temperature and pressure over 5% Pd/C (100mg) for 30 minutes. The mixture was filtered and evaporated to give the title compound (476mg, 100%); ν_{max} (CH_2Cl_2) 2952, 1733 and 1511cm^{-1}; δ_H [250MHz, $(CD_3)_2CO$, Me_4Si] 1.79 and 1.95 (4H, 2 x m, 2 x CH_2), 2.41 (2H, m, CH_2CO), 3.63 (3H, s, OMe), 4.01 (2H, m, OCH_2), 4.36 (2H, s, NCH_2), 6.85-7.31 (4H, m, Ar); *m/z* (EI$^+$) 237 (*M*$^+$, 55%).

d) **N-[4-(4-Methoxycarbonylbutyloxy)benzyl]monamide A** - The mixed anhydride of monic acid A (688mg, 2mmol) was treated with the product from Example 19c (474mg, 2mmol) as described in Example 5a to give, after chromatography, the title compound (425mg, 38%); ν_{max} (CH_2Cl_2) 3436 (br), 2929, 1732, 1666 and 1511cm^{-1}; δ_H (250MHz, CD_3OD, Me_4Si) 0.96 (3H, d, *J* 7Hz, 17-H_3), 1.21 (3H, d, *J* 6.5Hz, 14-H_3), 1.41 (2H, m, 12-H), 1.61-1.85 (6H, m, 9-H_2, 2 x CH_2), 1.96 (1H, m, 8-H), 2.10-2.25 (4H, m, 15-H_3, 4-H), 2.42 (2H, m, CH_2CO), 2.52-2.85 (3H, m, 4-H, 10-H, 11-H), 3.35-3.93 (6H, m, 5-H, 6-H, 7-H, 13-H, 16-H_2), 3.66 (3H, s, OCH_3), 3.98 (2H, m, OCH_2), 4.32 (2H, s, NCH_2), 5.79 (1H, s, 2-H), 6.87 and 7.21 (4H, ABq, *J* 8.6Hz, Ar); *m/z* (NH_3DCI^+) 564 (*M*H$^+$, 6%).

e) **N-[4-(4-Carboxybutyloxy)benzyl]monamide A** - The product from Example 19d (410mg) was converted to the title compound by the method described in Example 1e (353mg, 88%); ν_{max} (KBr) 3425 (br), 2927, 1715, 1659, 1624 and 1246cm^{-1}; δ_H (250MHz, CD_3OD, Me_4Si), 0.95 (3H, d, *J* 7Hz, 17-H_3), 1.21 (3H, d, *J* 6.5Hz, 14-H_3), 1.41 (2H, m, 12-H), 1.63-1.88 (6H, m, 9-H_2, 2 x CH_2), 1.97 (1H, m, 8-H), 2.10-2.26 (4H, m, 4-H, 15-H_3), 2.38 (2H, m CH_2CO), 2.55-3.87 (3H, m, 4-H, 10-H, 11-H), 3.36-3.93 (6H, m, 5-H, 6-H, 7-H, 13-H, 6-H_2), 4.00 (2H, m, OCH_2), 4.33 (2H, s, NCH_2), 5.79 (1H, s, 2-H), 6.88 and 7.21 (4H, ABq, *J* 8.6Hz, Ar); *m/z* (NH_3DCI^+), 550 (*M*H$^+$, 8%).

f) **N-{4-[4-(4-Methyl-1,2-dithiolo-[4,3-b]-5-(4H)oxopyrrol-6-ylamino-carbonyl)butyloxy]benzyl}monamide A** - The product from Example 19e (275mg) was converted to the title compound by the method described in Example 5b (80mg, 22%); ν_{max} (KBr) 3410 (br), 2928(br), 1661, 1640, 1511 and 1245cm^{-1}; λ_{max} (EtOH) 389.5 (ε_m 6,709), 309 (ε_m 2,867), 225.5 (ε_m 32,283); δ_H [250MHz, $(CD_3)_2SO$, Me_4Si] 0.82 (3H, d, *J* 7.4Hz, 17-H_3), 1.06 (3H, d, *J* 6.4Hz, 14-H_3), 1.31 (1H, m, 12-H), 1.57 (2H, m, 9-H_2), 1.61-1.88 (5H, m, 3'-H_2, 4'-H_2, 8-H), 1.98 (1H, m, 4-H), 2.10 (3H, s, 15-H_3), 2.35-2.78 (5H, m, 4-H, 10-H, 11-H, 2'-H_2). 3.12-4.33

(13H, m, 5-H, 6-H, 7-H, 13-H, 16-H_2, 5'-H_2 NCH_2, NCH_3), 4.50 (1H, d, *J* 4.6Hz, OH), 4.59 (1H, d, *J* 7.2Hz, OH), 4.73 (1H, d, *J* 3.1Hz), 5.70 (1H, s, 2-H), 6.87 and 7.15 (4H, ABq, *J* 8.6Hz, Ar), 7.35 (1H, s, 3"-H), 8.22 (1H, t, *J* 5.6Hz, N'-H), 10.00 (1H, s, N"-H); *m/z* (electrospray) 718 (MH^+, 100%).

Example 20 - N-{8-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]-octyl}monamide A

a) N-(7-Carboxyoctyl)monamide A - A solution of monic acid A (820g) in THF (10ml) at -10°C under argon was treated sequentially with triethylamine (0.36ml) and isobutyl chloroformate (0.31ml). The mixture was stirred for 30 minutes and treated with triethylamine (0.72ml) and 9-aminononanoic acid (0.5g) followed by enough water to give a clear solution. The mixture was stirred overnight at room temperature and then acidified to pH 3.5 with 5% citric acid solution. Extracted with ethyl acetate (2x). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was flash chromatographed on silica eluting with methanol/dichloromethane mixtures to give the title compound (520mg) as a mixture with monic acid A. δ_H (250MHz, CD_3OD, Me_4Si) *inter alia* 0.98 (3H, d, *J* 7Hz, 17-H_3), 1.22 (3H, d, *J* 6.4Hz, 14-H_3), 1.25-1.77 (15H, m, 9-H_2, 12-H, 6 x CH_2), 1.96 (1H, m, 8-H), 2.06-2.34 (6H, m, 4-H, 15-H_3, CH_2CO), 2.53-2.89 (3H, m, 4-H, 10-H, 11-H), 3.19 (2H, m, NCH_2), 3.26-3.95 (6H, m, 5-H, 6-H, 7-H, 16-H), 5.51 (1H, s, 2-H).

b) N-{8-[(4-Methyl-1,2-dithiolo-[4,3-b]-5-(4H)oxopyrrol-6-yl)-carbamoyl]-octyl}monamide A - The mixture from Example 20a (520mg) was converted to the title compound by the method described in Example 5b (190mg, 12% overall); ν_{max} (KBr) 3402 (br), 2925, 1653 and 1528cm^{-1}; λ_{max} (EtOH) 389.5 (ε_m 10,067), 311.5 (ε_m 3,990), 214.5 (ε_m 23,634); δ_H (250MHz, CD_3OD, Me_4Si) 0.96 (3H, d, *J* 7Hz, 17-H_3), 1.22 (3H, d, *J* 6.4Hz, 14-H_3), 0.97 (12H, m, 6 x CH_2), 1.52 (1H, m, 12-H), 1.69 (2H, m, 9-H_2), 1.96 (1H, m, 8-H), 2.16 (4H, m, 4-H, 15-H_3), 2.40 (2H, t, *J* 7.4Hz, CH_2CO), 2.51-2.87 (3H, m, 4-H, 10-H, 11-H), 3.19 (2H, t, *J* 6.8Hz), 3.23 (9H, m, 5-H, 6-H, 7-H, 13-H, 16-H, NMe), 5.75 (1H, s, 2-H), 7.27 (1H, s, 3"-H); δ_C (CD_3OD); 12.28 (C-17), 18.84 (C-15), 20.35 (C-14), 27.97 (NCH_3), 26.67, 28.07, 30.12, 30.21, 30.26, 30.43 (C-3', C-4', C-5', C-6', C-7', C-8'), 27.97 (C-NCH_3), 33.01 (C-9), 38.60 (C-2'), 40.10 (C-9'), 41.64 (C-8), 43.67 (C-4), 43.73 (C-12), 56.90 (C-10), 61.27 (C-11), 66.31 (C-16), 70.09 (C-6), 70.72 (C-13), 71.62 (C-7), 76.25 (C-5), 112.89 (C-3"), 115.42 (C-6a"), 121.31 (C-2), 135.88 (C-3a"), 137.58 (C-6"), 151.66 (C-3), 188.59 (C-5"), 189.65 (C-1), 174.23 (C-1'); *m/z* (EI^+). (Found M^+, 667.2969. $C_{32}H_{49}N_3O_8S_2$ requires *M* 667.2961).

Example 21 - N-{9-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]-nonyl}monamide A

a) **Triethylammonium N-(9-carboxynonyl)monamide A** - The mixed anhydride of monic acid A (550mg) was reacted with 10-aminodecanoic acid (360mg) as described in Example 5a to give the title compound (800mg) as a mixture with triethylammonium monate A; δ_H (250MHz, CD_3OD, Me_4Si) *inter alia* 0.96 (3H, d, *J* 7Hz, 17-H_3), 1.22 (3H, d, *J* 6.5Hz, 14-H_3), 1.25-1.75 (26H, m, 3 x CH_3, 7 x CH_2, 9-H_2, 12-H), 1.96 (1H, m, 8-H), 2.10-2.33 (6H, m, 4-H, 15-H, CH_2CO), 2.55-2.88 (3H, m, 4-H, 10-H, 11-H), 3.13-3.93 (5-H, 6-H, 7-H, 13-H, 16-H_2, NCH_2, 3 x NCH_2), 5.75 (1H, s, 2-H); *m/z* (NH_3DCI^+), 514 (MH^+, 5%).

b) **N-{9-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]-nonyl}monamide A** - The product from Example 21a (739mg) was converted to the title compound by the method described in Example 5b (190mg, 17% overall); ν_{max} (KBr) 3373 (br), 2926, 1659, 1531 and 1435cm^{-1}; λ_{max} (EtOH) 392.5 (ε_m 9,285), 315 (ε_m 3,399), 214.5 (ε_m 24,303); δ_H (250MHz, CD_3OD, Me_4Si) 0.96 (3H, d, *J* 7.1Hz, 17-H_3), 1.21 (3H, d, *J* 6.5Hz, 14-H_3), 1.27-1.75 (17H, m, 9-H_2, 12-H, 7 x CH_2), 1.98 (1H, m, 8-H), 2.13-2.25 (4H, m, 4-H, 15-H_3), 2.38 (2H, t, *J* 7.3Hz, CH_2CO), 2.55-2.87 (3H, m, 4-H, 10-H, 11-H), 3.16-3.93 (11H, m, 5-H, 6-H, 7-H, 13-H, 16-H_2, NCH_2, NCH_3), 5.75 (1H, s, 2-H), 7.27 (1H, s, 3"-H); δ_C (CD_3OD) 12.26 (C-17), 18.82 (C-15), 20.33 (C-14), 26.68, 27.99, 30.14, 30.23, 30.27, 30.39, 30.44 (C-3', C-4', C-5', C-6', C-7', C-8', C-9'), 28.04 (C-NCH_3), 32.99 (C-9), 36.59 (C-2'), 40.10 (C-10'), 41.62 (C-8), 43.64 (C-4), 43.71 (C-12), 56.89 (C-10), 61.26 (C-11), 66.30 (C-16), 70.07 (C-6), 70.70 (C-13), 71.60 (C-7), 76.23 (C-5), 112.90 (C-3"), 115.39 (C-6a"), 121.30 (C-2), 135.90 (C-3a"), 137.56 (C-6'), 151.62 (C-3), 166.59, 169.84 (C-1, C-5"), 174.24 (C-1'); *m/z* (electrospray) 682 (MH^+, 100%).

Example 22 - N-{10-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]-decyl}monamide A

a) **N-(10-Carboxydecyl)monamide A** - The mixed anhydride of monic acid A (688mg, 2mmol) was reacted with 11-aminoundecanoic acid (474mg, 2mmol) as described in Example 20a to give the title compound (200mg, 19%); δ_H (250MHz, CD_3OD, Me_4Si) 0.96 (3H, d, *J* 7Hz, 17-H_3), 1.21 (3H, d, *J* 6.4Hz, 14-H_3), 1.26-1.75 (19H, m, 9-H_2, 12-H, 8 x CH_2), 1.95 (1H, m, 8-H), 2.10-2.33 (6H, m, 4-H, 15-H, CH_2CO), 2.53-2.87 (3H, m, 4-H, 10-H, 11-H), 3.12-3.93 (8H, m, 5-H, 6-H, 7-H, 13-H, 16-H_2, NCH_2), 5.75 (1H, S, 2-H); *m/z* (NH_3DCI^+) 528 (MH^+, 28%).

b) N-{10-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]-decyl}monamide A - The product from Example 22a (200mg) was converted to the title compound by the method described in Example 5b (139mg, 53%); ν_{max} (KBr) 3411 (br), 2924, 1653 and 1531cm^{-1}; λ_{max} (EtOH) 391 (ε_m 10,547), 312 (ε_m 4,035), 212.5 (ε_m 24,511); δ_H (250MHz, CD_3OD, Me_4Si) 0.96 (3H, d, *J* 7.1Hz, 17-H_3), 1.21 (3H, d, *J* 6.5Hz, 14-H_3), 1.26-1.74 (19H, m, 9-H_2, 12-H, 8 x CH_2), 1.96 (1H, m, 8-H), 2.08-2.23 (4H, m, 4-H, 15-H_3), 2.54-3.85 (3H, m, 4-H, 10-H, 11-H), 3.18 (2H, t, *J* 6.8Hz, CH_2N), 3.28-3.91 (9H, m, 5-H, 6-H, 7-H, 13-H, 16-H_2, NCH_3), 5.74 (1H, s, 2-H), 7.27 (1H, s, 3"-H); δ_C (CD_3OD) 12.48 (C-17), 19.05 (C-15), 20.56 (C-14), 26.91, 28.26, 30.39, 30.52, 30.56, 30.64, 30.69, 30.74 (C-3', C-4', C-5', C-6', C-7', C-8', C-9', C-10'), 28.26 (C-NCH_3), 33.28 (C-9), 36.62 (C-2'), 40.33 (C-11'), 41.68 (C-8), 48.69 (C-4), 43.95 (C-12), 57.11 (C-10), 61.47 (C-11), 66.53 (C-16), 70.31 (C-6), 70.93 (C-13), 71.65 (C-7), 76.47 (C-5), 113.07 (C-3"), 115.65 (C-6a"), 121.53 (C-2), 136.12 (C-3a"), 137.61 (C-6"), 151.86 (C-3), 168.82 (C-5"), 169.67 (C-1), 174.47 (C-1'); *m/z* (FAB) (Found: MH^+ 696.2814. $C_{34}H_{54}N_3O_8S_2$ requires 696.3353).

Example 23 - N-{11-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-5-yl)carbamoyl]-undecyl}monamide A

a) N-(11-Carboxyundecyl)monamide A - The mixed anhydride of monic acid A (688mg, 2mmol) was reacted with 12-aminododecanoic acid (504mg, 2mmol) as described in Example 20a to give the title compound (135mg, 12%); δ_H (250MHz, CD_3OD, Me_4Si) 0.96 (3H, d, *J* 7.1Hz, 17-H_3), 1.22 (3H, d, *J* 6.4Hz, 14-H_3), 1.26-1.76 (21H, m, 9-H_2, 12-H, 9 x CH_2), 1.96 (1H, m, 8-H), 2.06-2.85 (6H, m, 4-H, 15-H_3, CH_2CO), 2.62-2.86 (3H, m, 4-H, 10-H, 11-H), 3.12-3.95 (8H, m, 5-H, 6-H, 7-H, 13-H, 16-H_2, NCH_2), 5.75 (1H, s, 2-H); *m/z* (NH_3DCI^+) 542 (MH^+, 100%).

b) N-{11-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-5-yl)carbamoyl]-undecyl}monamide A - The product from Example 23a was converted to the title compound by the method described in Example 5b (97mg, 60%); ν_{max} (KBr) 3404 (br), 2924, 1653 and 1538cm^{-1}; λ_{max} (EtOH) 391.5 (ε_m 9,918), 315.5 (4,172), 212.5 (26,196); δ_H (250MHz, CD_3OD, Me_4Si) 0.96 (3H, d, *J* 7Hz, 17-H_3), 1.21 (3H, d, *J* 6.4Hz, 14-H_3), 1.24-1.75 (2H, m, 9-H_2, 12-H, 9 x CH_2), 1.96 (1H, m, 8-H), 2.08-2.23 (4H, m, 4-H, 15-H_3), 2.40 (2H, t, *J* 6.9Hz, CH_2CO), 2.53-2.86 (3H, m, 4-H, 10-H, 11-H), 3.18 (2H, t, *J* 6.9Hz, NCH_2), 3.26-3.92 (9H, m, 5-H, 6-H, 7-H, 13-H, 16-H_2, NCH_3), 5.75 (1H, s, 2-H), 7.27 (1H, s, 3"-H); δ_C (CD_3OD) 12.28 (C-17), 18.85 (C-15), 20.35 (C-14), 26.71, 28.05, 30.19, 30.33, 30.40, 30.50, 30.55, 30.58 (C-3', C-4', C-5', C-6', C-7', C-8', C-9', C-10', C-11'), 28.05 (C-NCH_3), 33.03 (C-9), 36.62 (C-2'), 40.13 (C-12'), 41.67 (C-8), 43.68 (C-4), 43.75 (C-12), 56.91 (C-

10), 61.26 (C-11), 66.33 (C-16), 70.10 (C-6), 70.73 (C-13), 71.64 (C-7), 76.27 (C-5), 112.87 (C-3"), 115.44 (C-6a"), 121.32 (C-2), 135.93 (C-3a"), 137.60 (C-6"), 151.64 (C-3), 168.82 (C-5"), 169.88 (C-1), 174.23 (C-1'); *m/z* (FAB) (Found: MH^+ 710.3517, $C_{35}H_{56}N_3O_8S_2$ requires 710.3510).

Example 24 - N-{9-[(1,2-Dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]nonyl}monamide A

The product from Example 21a (710mg) was converted, by the method described in Example 10 to a product containing the title compound; ν_{max} (KBr) *inter alia* 3393 (br), 2970, 1653 and 1537cm^{-1}; δ_H (250MHz, CD_3OD, Me_4Si) *inter alia* 0.96 (3H, d, *J* 7Hz, 17-H_3), 1.21 (3H, d, *J* 6.4Hz, 14-H_3), 1.25-1.75 (17H, m, 9-H_2, 12-H, 7 x CH_2), 1.96 (1H, m, 8-H), 2.06-2.30 (4H, m, 4-H, 15-H_3), 2.40 (2H, t, *J* 7.3Hz, CH_2CO), 2.55-2.88 (3H, m, 4-H, 10-H, 11-H), 3.13-3.95 (8H, m, 5-H, 6-H, 7-H, 13-H, 16-H_2, NCH_2), 5.75 (1H, s, 2-H), 7.08 (1H, s, 3"-H); *m/z* (electrospray $^+$ve) 668.6 (MH^+, 100%).

Example 25 - E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran-2S-yl]-1-methylethylidene}-5[5-(4-methyl-1,2-dithiolo[4,3-b]-5-(4H)-oxopyrrol-6-yl)carbamoylpent-1-yloxy]indan-1-one

a) **2-Bromo-5-t-butyldimethylsilyloxybenzyl bromide** - 4-Bromo-3-methylphenol (4.49g, 24.0mmol), t-butyldimethylsilyl chloride (5.43g, 36.0mmol) and imidazole (4.90g, 22.0mmol) in N,N-dimethylformamide (30ml) were stirred at room temperature for 16h. Water (100ml) was added and the products extracted with ethyl acetate. Drying ($MgSO_4$), evaporation to dryness under reduced pressure and purification by flash chromatography using hexane as eluent gave the crude silylated phenol (4.16g, 57%). To this crude product (4.16g, 13.77mmol) was added N-Bromosuccinimide (2.70g, 15.15mmol) and carbon tetrachloride (100ml). The mixture was heated to reflux over a 150W light bulb for 2h. Cooling to 5°C, filtration, evaporation of the filtrate to dryness under reduced pressure and purification by flash chromatography using hexane as eluent gave the title compound as a colourless oil; δ_H ($CDCl_3$) 0.20 [6H, s, $Si(CH_3)_2$], 0.97 (9H, s, ^tBu), 4.50 (2H, s, CH_2Br), 6.63 (1H, dd *J* 2.9 and 8.5Hz, 4-H), 6.91 (1H, d, *J* 2.9Hz, 5-H), 7.37 (1H, d, *J* 8.5Hz, 3-H); *m/z* (E.I.) 382 (M^+, 5%), 380 (M^+, 10%), 378 (M^+, 5%); (Found: M^+, 377.9642. $C_{13}H_{20}Br_2OS$; requires M, 377.9652).

b) **E-2-{2-[3R,4R-*Bis*-trimethylsilyloxy-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran-3S-yl]-(1-methylethylidene)}-5-t-butyldimethylsilyloxyindan-1-one** - Diisopropylamine (0.16ml, 1.16mmol) and t-butyllithium (1.7M in hexane, 3.88ml, 6.60mmol) were added dropwise sequentially

to N-methoxy-N-methyl-6,7,13-O-tris(trimethylsilyl)monamide A (3.60g, 6.00mmol) in THF (30ml) maintaining the temperature below -65°C. After 1h at -70°C, 2-bromo-5-t-butyldimethylsilyloxy-benzyl bromide (3.01g, 7.90mmol) and lithium iodide (0.20g, 1.31mmol) were added and the mixture heated to reflux for 60h. The products were poured into water and extracted with ethyl acetate, dried (Na_2SO_4) and evaporated to dryness under reduced pressure. Removal of the excess benzyl bromide present by flash chromatography using hexane/ethyl acetate (6:1) as eluent gave a complex mixture (2.30g). This mixture was treated with t-butyllithium (1.7M in hexane) (3.30ml, 5.61mmol) in THF (20ml) at -70°C for 2h. Addition of water, extraction with ethyl acetate, drying (Na_2SO_4), evaporation to dryness under reduced pressure and purification by flash chromatography using hexane/ethyl acetate (7:1) as eluent gave a complex mixture containing the required deconjugated ketones (1.03g). This mixture was treated with potassium t-butoxide (0.20g, 1.60mmol) in THF (10ml) at -70°C for 2h. Acetic acid (0.16ml, 2.8mmol) then water were added. Extraction with ethyl acetate, drying (Na_2SO_4), evaporation to dryness under reduced pressure and purification by flash chromatography using hexane/ethyl acetate (8:1) as eluent gave the title compound (0.63g, 14%) as a white foam; δ_H (CD_3OD) 0.10-0.27 (33H, m, 11 x $SiCH_3$), 0.92 (3H, d, *J* 7.0Hz, 17-H_3), 1.01 (9H, s, ^tBu), 1.20 (3H, d, *J* 6.3Hz, 14-H_3), 1.28-1.42 (1H, m, 12-H), 1.67-1.83 (3H, m, 9-H_2 and 8-H), 2.36 (1H, dd, *J* 13.4 and 10.5Hz, 4-H), 2.40 (3H, s, 15-H_3), 2.58 (1H, d, *J* 13.4Hz, 4-H), 2.72-2.82 (2H, m, 10 and 11-H), 3.50-3.95 (8H, m, 5,7,13, 16-H, 16-H_2 and CH_2Ph), 6.87 (1, dd, *J* 8.3 and 2.0Hz, phenyl), 6.93 (1H, d, *J* 2.0Hz, phenyl), 7.63 (1H, d, *J* 8.3Hz, phenyl); *m/z* 762 (M^+, 13%), 173 (100%); (Found: M^+, 762.4209. $C_{39}H_{70}O_7Si_4$ requires M. 762.4199).

c) **E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran-2S-yl]-(1-methylethylidene)}-5-hydroxyindan-1-one** - The ketone from Example 25b (0.62g, 0.81mmol) was treated with tetra-n-butylammonium fluoride in THF (15ml) at 5°C for 10 mins. Addition of a pH 7 buffer solution (20ml), extraction with ethyl acetate, drying (Na_2SO_4) evaporation to dryness under reduced pressure, and purification by flash chromatography using 10% methanol in dichloromethane as eluent gave the title compound (0.34g, 97%) as a white foam; υ_{max} (KBr) 3423, 2966, 2927, 1669, 1623, 1585, 1304, 1266, 1093cm^{-1}; λ_{max} (EtOH) 312nm (ε_m 16,596) and 293.5nm (sh) (ε_m 14,072); δ_H (CD_3OD) 0.94 (3H, d, *J* 7.1Hz, 17-H_3), 1.19 (3H, d, *J* 6.4Hz, 14-H_3), 1.33-1.44 (1H, m, 12-H), 1.61-1.83 (2H, m, 9-H_2), 1.87-1.97 (1H, m, 8-H), 2.40 (2H, s, 15-H_3), 2.45 (1H, dd, *J* 13.6 and 9.6Hz, 4-H), 2.72-2.84 (3H, m, 4, 10 and 11-H), 3.40 (1H, dd, *J* 9.3 and 3.0Hz, 6-H), 3.53 (1H, d, *J* 11.6Hz, 16-H), 3.50-3.94 (6H, m, 5,7,13, 16-H and CH_2Ph), 6.77 (1H, dd, *J* 2.1, 8.3Hz, phenyl), 6.80 (1H, d, *J* 2.1Hz, phenyl),

(1H, d, *J* 8.3Hz, phenyl); δ_C (CD_3OD) 12.2 (C-17), 18.7 (C-14), 20.3 (C-15), 32.9 (CH_2Ph), 33.0 (C-9), 41.6 (C-4), 41.7 (C-8), 43.6 (C-12), 56.8 (C-10), 61.3 (C-11), 66.4 (C-16), 70.3 (C-6), 70.7 (C-7), 71.6 (C-13), 76.9 (C-5), 112.3, 116.8, 126.6, 133.5 (q), 133.6 (q), 151.2 (q), 153.3 (q), 164.9 (q), 195.1 (C-1); *m/z* 432 (M^+, 4%); (Found: M^+, 432.2158. $C_{24}H_{32}O_7$ requires M, 432.2148).

d) E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran-2S-yl]-1-methylethylidene}-5-(methoxycarbonylpent-1-yloxy)indan-1-one - The product from Example 25c (0.5g, 1.15mmol) was dissolved in THF (5ml) and added to a suspension of sodium hydride (43mg, 1.04mmol) in THF (3ml). The mixture was stirred under an atmosphere of argon for 10mins. Methyl 6-iodohexanoate (0.3g, 1.15mmol) in THF (3ml) was added followed by DMF (5ml) and 15-crown-5 (0.1g, 0.58mmol). The resulting solution was stirred for 48 hours. The mixture was poured into water and extracted with ethyl acetate. The combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography eluting with 5% methanol in dichloromethane to afford the title compound as a white solid (250mg, 39%); υ_{max} (KBr) 3422, 2924, 1735, 1681, 1623cm^{-1}; λ_{max} (EtOH) 309.5nm (ε_m 22,954), 239.5nm (ε_m 7,265); δ_H (CD_3OD) 0.96 (3H, d, *J* 7.1Hz, 17-H_3), 1.2 (3H, d, *J* 6.5Hz, 14-H_3), 1.29-2.0 (10H, m, 9H_2, 8, 12-H and 3xCH_2), 2.37 (2H, t, *J* 7.3Hz, CH_2), 2.42 (3H, s, 15-H_3), 2.5 (1H, d, *J* 9.7Hz, 4-H), 2.64-2.85 (3H, m, 10, 4 and 11-H), 3.41 (1H, dd, *J* 3.2 and 9.2Hz, 6-H), 3.55 (1H, d, *J* 11.6Hz, 16-H), 3.63 (3H, s, OCH_3), 3.69-3.92 (6H, m, 7, 5, 13, 16 and CH_2-Ph), 4.08 (2H, t, *J* 6.3Hz, CH_2), 6.91 (1H, dd, *J* 2.2 and 8.6Hz, Ar-H), 6.99 (1H, d, *J*2.2Hz, Ar-H), 7.61 (1H, d, *J* 8.6Hz, Ar-H); *m/z* (FAB, thioglycerol)(MH^+) 561.

e) E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl) tetrahydropyran-2S-yl]-1-methylethylidene}-5-(5-carboxypent-1-yloxy)indan-1-one - The methyl ester from Example 25d (10mg, 0.018mmol) was stirred in pH 7 buffer Na_2HPO_4 (9ml) and acetone (1ml). Subtilisin Carlsburg (6mg) was added and the resulting suspension was stirred for 48 hours. The solvent was removed by freeze drying. The residue was treated with ethanol (25ml) and filtered. The filtrate was evaporated and the resulting solid was dissolved in water and acidified to pH 3. The products were extracted with ethyl acetate and the combined organic extracts were washed with water, dried with anhydrous magnesium sulphate, and the solvent removed to give the desired product as a white solid (7.3mg, 75%); δ_H (CD_3OD) 0.95 (3H, d, *J* 7.1Hz, 17-H_3), 1.21 (3H, d, *J* 6.5Hz, 14-H_3), 1.29-2.0 (10H, m, 9-H_2, 8 and 12-H and 3xCH_2), 2.31 (2H, t, *J* 7.3Hz, CH_2), 2.42 (3H, s, 15-H_3), 2.48 (1H, d, *J* 9.7Hz, 4-H), 2.69-2.88 (3H, m, 4, 10 and 11-H), 3.41 (1H, dd, *J* 3.0Hz and 9.2Hz, 6-H), 3.53 (1H, d, *J* 11.5Hz, 16-H), 3.69-3.93 (6H, m, 5, 7, 13, 16 and

CH_2Ph), 4.08 (2H, t, *J* 6.4Hz, CH_2), 6.92 (1H, dd, *J* 2.2 and 8.5Hz, Ar-H), 7.0 (1H, d, *J* 2.2Hz, Ar-H), 7.63 (1H, d, *J* 8.5Hz, Ar-H).

f) **E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl) tetrahydropyran-2S-yl]-1-methylethylidene}-5-[5-(4-methyl-1,2-dithiolo[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylpent-1-yloxy]indan-1-one** - To the acid from Example 25e (58mg, 1.06 x 10^{-4}moles) in dry THF (10ml), under an atmosphere of argon, triethylamine (0.016ml, 1.16 x 10^{-4}moles 1.1eq.), followed by isobutylchloroformate (0.014ml, 1.06 x 10^{-4}moles) were added, maintaining the external temperature at -20°C. After ½hour, a further portion of triethylamine (0.03ml, 2.12 x 10^{-4}moles, 2eq.) followed by 6-amino-4-methyl-1,2-dithiolo[4,3-b]pyrrol-5(4H)-one hydrochloride (W.D. Celmer and I.A. Solomons, *J.Amer.Chem.Soc.*, 1955, 77, 2861) (30mg, 1.27 x 10^{-4}moles, 1.2eq.) was added and the resultant solution allowed to warm up to room temperature. After 22hours the reaction was diluted with ethyl acetate, washed with water, $NaHCO_3$ and brine, dried over anhydrous magnesium sulphate, and the solvent removed. The crude product was purified by flash chromatography on silica gel eluting with 3% methanol in dichloromethane to give the title compound as a yellow solid (25mg, 33%); λ_{max} (EtOH) 391.5 (ε_m 9041), 309.0 (ε_m 22,989), 271 (ε_m 13,877), 233.0 (ε_m 13,107); δ_H [$(CD_3)_2SO$] 0.82 (3H, d, *J* 7.1Hz, 17-H_3), 1.08 (3H, d, *J* 6.4Hz, 14-H_3), 1.2-1.9 (10H, m, 3 x CH_2, 9Hz, 8, 12-H), 2.3 (1H, dd,*J*13.4 and 9.4Hz, 4-H), 2.36 (3H, s, 15-H_3), 2.39 (2H, t, *J* 7.2Hz, CH_2), 2.6-2.75 (3H, m, 4, 10, 11-H), 3.25 (3H, s, NCH_3), 3.38-3.79 (6H, m, 6, 7, 5, 13-H, 16-H_2), 4.05 (2H, t, *J* 6.4Hz, CH_2), 4.45 (1H, d, *J* 2.7Hz, OH), 4.62 (1H, d, *J* 7.6Hz, OH), 4.75 (1H, d, *J* 3.4Hz, OH), 6.95 (1H, dd, *J* 2.1 and 8.5Hz, Ar-H), 7.05 (1H, d, *J* 1.7Hz, Ar-H), 7.32 (1H, s, 3"-H), 7.55 (1H, d, *J* 8.5Hz, Ar-H), 9.92 (1H, s, N-H); *m/z* (NH3 DCI)(MH^+) 715.

Example 26 - E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran-2S-yl]-1-methylethylidene}-5-[3-(4-methyl-1,2-dithiolo[4,3-b]-5-(4H)-oxopyrrol-6-yl)carbamoylprop-1-yl]indan-1-one

a) **E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl) tetrahydropyran-2S-yl]-1-methylethylidene}-5-(3-methoxycarbonylprop-1-yloxy)-indan-1-one** - The product from Example 25c (0.53g, 1.22 x 10^{-3}moles) was dissolved in dry DMF (5ml) and added to a suspension of sodium hydride (44mg, 1.09 x 10^{-3}moles, 0.9eq.) in dry DMF (3ml). After 20 minutes, methyl 4-iodobutanoate (0.27g, 1.22 x 10^{-3}moles) was added in dry DMF (1ml). After 1hour, a further portion of methyl-4-iodobutanoate (0.06g, 2.7 x 10^{-4}moles, 0.2eq.) was added and the resulting solution stirred for 22hours. Water was added and the products extracted into ethyl acetate. The combined organic extracts were washed with water

and brine, dried over anhydrous magnesium sulphate and evaporated to dryness. The crude products were purified by flash chromatography on silica gel eluting with 5% methanol in dichloromethane to give the title compound as a white solid (0.32g, 52%); υ_{max} (KBr) 3421, 2959, 1735, 1680, 1623cm^{-1}; λ_{max} (EtOH) 308.0nm (ε_m 23,033), 239.0nm (ε_m 6,998); δ_H (CD_3OD) *inter alia* 0.93 (3H, d, *J* 7.1Hz, 17-H_3), 1.2 (3H, d, *J* 6.4Hz, 14-H_3), 2.41-2.50 (4H, m, 15-H_3, 4-H), 2.53 (2H, t, *J* 7.3Hz, CH_2), 2.7-2.88 (3H, m, 4, 10, 11-H), 3.41 (1H, d, *J* 9.2Hz and 3.1Hz, 6-H), 3.55 (1H, d, *J* 11.5Hz, 16-H), 3.69 (3H, s, OCH_3), 3.7-3.92 (6H, m, 7, 5, 13, 16-H, CH_2), 4.1 (2H, t, *J* = 6.2Hz, CH_2), 6.9 (1H, dd, *J* 2.1 and 8.5Hz, Ar-H), 7.01 (1H, d, *J* 2.1Hz, Ar-H), 7.63 (1H, d, *J* 8.5Hz, Ar-H); *m/z* (EI) (Found: M^+, 532.2679; $C_{29}H_{40}O_9$ requires M, 532.2672).

b) E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl) tetrahydropyran-2S-yl]-1-methylethylidene}-5-(3-carboxyprop-1-yloxy)indan-1-one - The methyl ester from Example 26a (310mg, 5.8 x 10^{-4}moles) was stirred in pH 7 buffer Na_2HPO_4 (279ml) and acetone (31ml). Subtilisin Carlsburg (50mg) was added and the resulting suspension stirred for 48hours. The volume was reduced *in vacuo* to ~150ml and ethyl acetate was added. The pH was adjusted to 3.5 with 1.5M H_3PO_4. The products were extracted into ethyl acetate and washed with water and brine, dried over anhydrous magnesium sulphate and evaporated to dryness to give the title compound as a white solid (0.24g, 80%); υ_{max} (KBr) 3429, 2892, 1680, 1621, 1607cm^{-1}; λ_{max} (EtOH) 310.0 (ε_m 22,715), 239.0 (ε_m 7,171); δ_H (CD_3OD) *inter alia* 0.95 (3H, d, *J* 7.1Hz, 17-H_3), 1.2 (3H, d, *J* 6.2Hz, 14-H_3), 2.4-2.55 (6H, m, 15-H_3, CH_2, 4-H), 2.7-2.85 (3H, m, 10, 11, 4-H), 3.45 (1H, dd, *J* 3.1 and 9.2Hz, 6-H), 3.55 (1H, d, *J* 11.5Hz, 16-H), 3.7-3.92 (6H, m, 6, 5, 7, 13-H, CH_2), 4.15 (2H, t, *J* 6.3Hz, CH_2), 6.95 (1H, dd, *J* 2.1 and 8.5Hz, Ar-H), 7.05 (1H, d, *J* 2.1Hz, Ar-H), 7.65 (1H, d, *J* 8.5Hz, Ar-H); *m/z* (NH3 DCI)(*M*H$^+$) 519.

c) E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl) tetrahydropyran-2S-yl]-1-methylethylidene}-5-[3-(4-methyl-1,2-dithiolo[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylprop-1-yloxy]indan-1-one - To the acid from Example 26b (0.21g, 4.05 moles) in dry THF (25ml) under an atmosphere of argon, triethylamine (0.065ml, 4.45 x 10^{-4}moles, 1.1eq.) followed by isobutylchloroformate (0.055ml, 4.05 x 10^{-4}moles) were added, maintaining the external temperature at -20°C. After ½hour, a further portion of triethylamine (0.1ml, 9.1 x 10^{-4}moles, 2eq.) was added followed by 6-amino-4-methyl-1,2-dithiolo[4,3-b]pyrrol-5(4H)-one hydrochloride (0.1g, 4.5 x 10^{-4}moles, 1.2eq.). The reaction was allowed to warm up to room temperature and after 22hours, was diluted with ethyl acetate, washed with $NaHCO_3$, water and brine and dried over anhydrous magnesium sulphate. Evaporation of the solvent gave the crude product which was purified by flash

chromatography on silica gel eluting with 2%→5% methanol in dichloro-methane to give the title compound as a yellow solid (0.09g, 33%); υ_{max} (KBr) 3415, 3252, 3044, 1673, 1644, 1597, 1532cm^{-1}; λ_{max} (EtOH) 391.0 (ε_m 9,952), 308.5 (ε_m 25,582), 232.0 (ε_m 12,756); δ_H [$(CD_3)_2SO$] *inter alia* 0.81 (3H, d, *J* 7.0, 17-H_3), 1.08 (3H, d, *J* 6.4Hz, 14-H_3), 2.25-2.4 (4H, m, 4-H, 15-H_3), 2.5-2.8 (5H, m, CH_2, 4, 10, 11-H), 3.25 (3H, s, NCH_3), 4.1 (2H, t, *J* 6.9Hz, CH_2), 4.5 (1H, d, *J* 4.6Hz, OH), 4.67 (1H, d, *J* 7.6Hz, OH), 4.78 (1H, d, *J* 3.3Hz, OH), 6.9 (1H, d, *J* 8.5Hz, Ar-H), 7.05 (1H, s, Ar-H), 7.32 (1H, s, 3"-H), 7.6 (1H, d, *J* 8.5Hz, Ar-H), 10.0 (1H, s, N-H); *m/z* (Electrospray)(*M*H$^+$) 687.

Example 27 - E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl) tetrahydropyran-2S-yl]-1-methylethylidene}-5-[1-(4-methyl-1,2-dithiolo[4,3-b]-5-(4H)-oxopyrrol-6-yl)carbamoylmethoxy]indan-1-one

a) E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl) tetrahydropyran-2S-yl]-1-methylethylidene}-5-(methoxycarbonyl methoxy)indan-1-one - The product from Example 25c (0.56g, 1.29 x 10^{-3}moles) in dry DMF (5ml) was added slowly to a suspension of sodium hydride (45mg, 1.2 x 10^{-3}moles 0.9eq.) in dry DMF (1ml). After 20mins., methyl bromoacetate (0.23g, 1.58 x 10^{-3}moles, 1.2eq.) was added and the resulting solution was stirred under an atmosphere of argon for 5hours. Water was added and the products extracted into ethyl acetate. The combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulphate and evaporated to dryness. The crude products were purified by flash chromatography on silica gel eluting with 2% methanol in dichloromethane to give the title compound as a white solid (0.18g, 28%); υ_{max} (KBr) 3455, 1750, 1680, 1606cm^{-1}; λ_{max} (EtOH) 301.0nm (ε_m 21,523), 232.5nm (ε_m 6,842); δ_H (CD_3OD) 0.98 (3H, d, *J* 7.1Hz, 17-H_3), 1.2 (3H, d, *J* 6.4Hz, 14-H_3), 1.35-1.50 (1H, m, 12-H), 1.63-1.88 (2H, m, 9H_2), 1.9-2.02 (1H, m, 8-H), 2.4-2.52 (4H, m, 15-H_3, 4-H), 2.7-2.9 (3H, m, 4, 10, 11-H), 3.44 (1H, dd, *J* 3.1Hz and 9.2Hz, 6-H), 3.56 (1H, d, *J* 11.5Hz, 16-H), 3.7-4.0 (9H, m, 13, 5, 16, 7-H, CH_2 & OCH_3), 4.71 (2H, s, CH_2), 6.95-7.05 (2H, m, Ar-H_2), 7.69 (1H, d, *J* 8.4Hz, Ar-H); *m/z* (EI)(Found: M$^+$, 504.2365; $C_{27}H_{36}O_9$ requires M, 504.2361).

b) E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl) tetrahydropyran-2S-yl]-1-methylethylidene}-5-(1-carboxymethoxy)indan-1-one - The methyl ester from Example 27a (310mg, 6.15 x 10^{-4}moles) was stirred in pH7 buffer Na_2HPO_4 (279ml) and acetone (31ml). Subtilisin Carlsburg (50mg) was added and the resulting suspension stirred for 16hours. The volume was reduced in vacuo to ~150ml and ethyl acetate was added. The pH was adjusted to 3.5 with 1.5M H_3PO_4. The products were extracted into ethyl acetate and washed with water and

brine, dried over anhydrous magnesium sulphate and evaporated to dryness to give the title compound as a white solid (0.22g, 70%); υ_{max} (KBr) 3421, 2855, 1735, 1679, 1622, 1600cm^{-1}; λ_{max} (EtOH) 311.5nm (ε_m 9,560), 273.0 (ε_m 5,129), 241.0nm (ε_m 3,205); δ_H (CD_3OD) *inter alia* 0.97 (3H, d, *J* 7.1Hz, 17-H_3), 1.2 (3H, d, *J* 6.4Hz, 14-H_3), 2.40-2.55 (4H, m , 15-H_3, 4-H), 2.7-2.9 (3H, m, 4, 10, 11-H), 3.45 (1H, dd, *J* 3.1Hz and 9.2Hz, 6-H), 3.55 (1H, d, *J* 11.6Hz, 16-H), 3.7-4.0 (6H, m, 6, 5, 7, 13-H, CH_2), 4.79 (2H, s, CH_2), 6.98-7.10 (2H, m, Ar-H_2), 7.0 (1H, d, Ar-H), 7.7 (1H, d, *J* 8.3Hz, Ar-H); *m/z* (NH3 DCI)(*M*H$^+$) 491.

c) **E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl) tetrahydropyran-2S-yl]-1-methylethylidene}-5-{1-(4-methyl-1,2-dithiolo[4,3-b]-5-(4H)-oxopyrrol-6-yl)carbamoylmethoxy]indan-1-one** - To the acid from Example 27b (0.2g, 4.08 x 10^{-4}moles) in dry THF (10ml), under an atmosphere of argon, triethylamine (0.056ml, 4.08 x 10^{-4}moles) followed by isobutylchloroformate (0.05ml, 4.08 x 10^{-4}moles) were added maintaining the external temperature at -20°C. After ½hour, a further portion of triethylamine (0.1ml, 8.16 x 10^{-4}moles, 2eq.) was added followed by 6-amino-4-methyl-1,2 dithiolo[4,3-b]pyrrol-5(4H)-one hydrochloride (0.1g, 4.4 x 10^{-4}moles, 1.1eq.). The reaction was allowed to warm up to room temperature and after 22hours, it was evaporated to dryness.The crude product was purified by flash chromatography on silica gel eluting with 2% methanol in dichloromethane. Triethylamine hydrochloride was removed by trituration with dichloromethane, filtration gave the title compound as a yellow solid (70mg, 27%); υ_{max} (KBr) 3384, 1670, 1599, 1528cm^{-1}; λ_{max} (EtOH) 394.5nm (ε_m 11,083), 302.0nm (ε_m 25,132), 266.5nm (ε_m 12,818); δ_H [$(CD_3)_2$)SO]*inter alia* 0.85 (3H, d, *J* 7.0Hz, 17-H_3), 1.05 (3H, d, *J* 6.4Hz, 14-H_3), 1.30-1.40 (1H, m, 12-H), 1.48-1.70 (2H, m, 9-H_2), 1.75-1.85 (1H, m, 8-H), 2.28-2.38 (4H, m, 15-H_3, 4-H), 2.55-2.8 (3H, m, 4, 10, 11-H), 3.4 (1H, d, *J* 11.0Hz, 16-H), 3.6-3.8 (6H, m, 5, 6, 7, 13, CH_2), 4.45 (1H, d, *J* 4.6Hz, OH), 4.6 (1H, d, *J* 7.5Hz, OH), 4.7 (1H, d, *J* 3.3Hz, OH), 4.9 (2H, s, CH_2), 6.95 (1H, dd, *J* 8.4Hz and 1.8Hz, Ar-H), 7.05 (1H, d,*J*1.8HzAr-H), 7.4 (1H, s, CH), 7.6 (1H, d, *J* 8.5Hz, Ar-H), 10.15 (1H, s, NH).

Example 28 - E-2-{2-[3R,4R-Dihydroxy-5S(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran-2S-yl]-1-methylethylidene}5-[1-(1,2-dithiolo[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylmethoxy]indan-1-one - To the acid from Example 27b (160mg, 3.38 x 10^{-4}mmol) in dry THF (10ml) under an atmosphere of argon, triethylamine (0.052ml, 3.7 x 10^{-4}moles) followed by isobutylchloroformate (0.044ml, 3.38 x 10^{-4}moles) was added maintaining the external temperature below -20°C. After ½hour, triethylamine (0.095ml, 6.7 x 10-^{4}moles), followed by 6-amino-1,2-dithiolo [4,3-b] pyrrol-5(4H) one hydrochloride (85mg, 3.72 x 10-^{4}moles) was

added. The reaction was allowed to warm to room temperature. After 2 hours ethyl acetate was added and the products were washed with water and brine, dried over anhydrous magnesium sulphate and evaporated to dryness. The crude products were purified by flash chromatography on silica gel eluting with 2% methanol in dichloromethane giving the title compound as a yellow solid (20mg, 10%); ν_{max} (KBr) 3422, 3052, 1660, 1598cm^{-1}; λ_{max}(EtOH) 382nm (ε_m 6,543), 294.5nm (ε_m 12,951); δ_H [$(CD_3)_2SO$]; 0.85 (3H, d, *J* 7.02Hz, 17-H_3), 1.05 (3H, d, *J* 6.4Hz, 14-H_3), 1.2-1.9 (4H, m, 8, 12-H, 9H_2), 2.4 (4H, m, 15-H_3, 4H), 2.6-2.8 (3H, m, 4, 10, 11-H), 3.6-3.8 (6H, m, 16, 5, 7, 13-H, CH_2), 4.50 (1H, d, *J* 4.6Hz, O*H*), 4.65 (1H, d, *J* 7.5Hz, O*H*), 4.75 (1H, d, *J* 3.2Hz, O*H*), 4.95 (2H, s, CH_2), 6.95 -7.10(2H, m, *J* 8.2Hz, Ar-H_2), 7.15 (1H, s, C*H*), 7.6 (1H, d, *J* 8.5Hz, Ar-H), 10.1 (1H, br s, N*H*), 10.8 (1H, br s, N*H*); *m/z* (Electrospray)(*M*H$^+$), 645.3.

Example 29 - E-2-{2[5(5S-Hydroxy-4R-methylhex-2-enyl)-3R,4R-dihydroxytetrahydropyran-2S-yl]-1-methylethylidene}5-[1-(1,2-dithiolo[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl-methoxy]indan-1-one

a) 2-Bromo-5-t-butyldimethylsilyloxybenzyl iodide - To 2-bromo-5-t-butyldimethylsilyoxybenzyl bromide from Example 25a (2g, 5.2mmol) in acetone (40ml), sodium iodide (7.9g, 52mmol) was added. The resultant solution was stirred for 24 hours. It was then filtered and evaporated to dryness. The crude product was dissolved in dichloromethane (40ml) and washed with 10% sodium thiosulphate solution, water, and brine. It was then dried over anhydrous magnesium sulphate, filtered, and evaporated to dryness, to give title compound as a colourless oil (2.12g, 95%); δ_H ($CDCl_3$); 0.19 (6H, s, Si$(CH_3)_2$), 0.98 (9H, s, t-Bu), 4.43 (2H, s, CH_2), 6.62 (1H, dd, *J* 2.9Hz, and 8.7Hz, Ar-H), 6.91 (1H, d, *J* 2.9Hz, Ar-H),7.4 (1H, d, *J* 2.8Hz, Ar-H), 7.35 (1H, d, *J* 8.7Hz, Ar-H).

b) E-2-{2[5(5S-Trimethylsilyloxy-4R-methylhex-2E-enyl)-3R,4R-bistrimethylsilyloxytetrahydropyran-2S-yl]-1-methylethylidene}5-t-butyldimethylsilyloxyindan-1-one - Di-*iso*-propylamine (0.08ml, 0.63mmol) and t-butyllithium (1.7M in pentane) (2.2ml, 3.8mmol) were added dropwise sequentially to N-methoxy-N-methyl-6, 7, 13-O-tris(trimethylsilyl)monamide C (1.87g, 3.17mmol) (Example 4a) in dry THF (20ml), maintaining the temperature below -65°C. After 1 hour at -70°C, 2-bromo-5-t-butyldimethylsilyloxybenzyl iodide from Example 29a (2g, 4.7mmol) was added, and the mixture stirred at -70°C for 1 hour. The temperature was slowly raised to room temperature over 2 hours. Saturated ammonium chloride solution (10ml) was added and the products were extracted into ethyl acetate, washed with water and brine, dried over anhydrous magnesium sulphate and evaporated to dryness. The crude products were purified by flash

chromatography on silica gel eluting with hexane/ethyl acetate (6:1) to give a complex mixture (1.75g). This mixture was treated with t-butyllithium (1.7M in pentane) (2.6ml, 4.4mmol) in dry THF (15ml) at -70°C for 2 hours. Saturated ammonium chloride solution (10ml) was added and the products were extracted into ethyl acetate, washed with water and brine, dried over anhydrous magnesium sulphate, and evaporated to dryness, to give a complex mixture (1.4g). This mixture was treated with potassium t-butoxide (1M) (2.5ml, 2.5mmol) in dry THF (15ml) at -70°C for 2 hours. Acetic acid (0.16ml) followed by water was added. The products were extracted with ethyl acetate, washed with water and brine, dried over anhydrous magnesium sulphate and evaporated to dryness. The crude products were purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (96:4) to give title compound as a white foam (0.8g, 34%); δ_H ($CDCl_3$) *inter alia* 0.1-0.3 (33H, m, Si-CH_3), 1.05 (3H, d, *J* 6.1Hz, 14-H_3), 2.45 (3H, s, 15H_3), 2.55 (1H, d, 4H), 5.35-5.42 (2H, m, 10, 11-H), 6.78-6.88 (1H, dd, Ar-H), 7.69 (1H, d, *J* 8.2Hz, Ar-H).

c) **E-2-{2[5(5S-Hydroxy-4R-methylhex-2E-enyl)-3R,4R-dihydroxy-tetrahydropyran-2S-yl]-1-methylethylidene}-5-hydroxyindan-1-one** - To the product from Example 29b (0.75g, 1mmol) in THF (10ml), tetrabutylammonium fluoride (5ml, 5mmol) was added and the resultant solution stirred for 30 minutes. pH 7 buffer was added and the products were extracted into ethyl acetate, washed with water and brine, dried over anhydrous magnesium sulphate and evaporated to dryness. The crude product was purified by flash chromatography on silica gel eluting with 5% methanol in dichloromethane to give title compound as a white foam (0.34g, 82%); ν_{max} (KBr) 3424, 1673, 1622, 1598 cm^{-1}; λ_{max} (EtOH) 310.0nm (ε_m 14,150), 293 (ε_m 11,868), 271 (ε_m 7,760); δ_H (CD_3OD) *inter alia* 1.0 (3H, d, *J* 6.9Hz, 17-H_3), 1.09 (3H, d, *J* 6.4Hz, 14-H_3), 1.78 (1H, m, 8H), 2.35-2.48 (4H, m, 4-H, 15-H_3), 3.49-3.9 (8H, m, 16-H_2, 6, 5,7, 13-H, CH_2), 5.45 (2H, s, CH_2), 5.42-5.50 (2H, m, 10, 11-H), 6.75-6.85 (2H, m, Ar-H_2), 7.49 (1H, d, *J* 8.3Hz, Ar-H); *m/z* (EI)(M^+), 416.

d) **E-2-{2[5(5S-Hydroxy-4R-methylhex-2E-enyl)-3R,4R-dihydroxy-tetrahydropyran-2S-yl]-1-methylethylidene}5-(1 methoxycarbonylmethoxy)indan-1-one** - To the product from Example 29c (320mg, 0.77mmol) in dry DMF (10ml), tetramethylguanidine (0.14ml, 1.15mmol) was added followed by methyl bromo-acetate (0.1ml, 1.15mmol). The resulting solution was stirred under an atmosphere of argon for 45 minutes. Water was added and the products were extracted into ethyl acetate, washed with water and brine, dried over anhydrous magnesium sulphate and evaporated to dryness. The crude products were purified by flash chromatography on silica gel eluting with 3% methanol in dichloromethane to give the title compound as a white foam (290mg, 78%); ν_{max}

(KBr) 3426, 1760, 1674, 1624, 1601, cm^{-1}. λ_{max} (EtOH) 301.0nm (ε_m 21,304), 231.0nm (ε_m 6,633); δ_H (CD_3OD) 1.0 (3H, d, *J* 6.9Hz, 17-H_3), 1.09 (3H, d, *J* 6.4Hz, 14-H_3), 1.76 (1H, m, 8-H), 2.1-2.3 (3H, m, 9H_2, 12-H), 2.4-2.52 (4H, m, 15-H_3, 4H), 2.75 (1H, d, *J* 12.2Hz, 4-H), 3.4-3.9 (11H, m, 16-H_2, 6, 5, 7, 13-H, OCH_3, CH_2), 4.85 (2H, s, CH_2), 5.42-5.50 (2H, m, 10, 11-H), 6.98-7.06 (2H, m, Ar-H_2), 7.65 (1H, d, *J* 8.4Hz, Ar-H); *m/z* (EI)(M^+), 488.

e) **E-2-{2[5(5S-Hydroxy-4R-methylhex-2E-enyl)-3R,4R-dihydroxy-tetrahydropyran-2S-yl]-1-methylethylidene}-5-(1-carboxymethoxy)indan-1-one** - To the methylester from Example 29d (270mg, 5.5mmol) in acetone (27ml) and pH 7 buffer Na_2HPO_4 (243ml), Subtilisin Carlsberg (50mg) was added and the resulting suspension stirred for 24 hours. The volume was reduced *en vacuo* to ~150ml and ethyl acetate was added. The pH was adjusted to 3.5 with 1.5M. H_3PO_4. The products were extracted into ethyl acetate and washed with water and brine, dried over anhydrous magnesium sulphate and evaporated to dryness to give title compound as a white solid (240mg, 91%); ν_{max} (KBr) 3434, 2924, 1736, 1674,1622,1600 cm^{-1}; λ_{max} (EtOH) 311.5nm (ε_m 22,755), 241.0nm (8,448); δ_H (CD_3OD) 1.0 (3H, d, *J* 6.9Hz, 17-H_3), 1.09 (3H, d, *J* 6.3Hz, 14-H_3), 1.78 (1H, m, 8H), 2.25 (3H, m, 9H_2, 12-H), 2.45 (4H, m, 15-H_3, 4-H), 2.79 (1H, d, *J* 13.5Hz, 4-H), 3.4-3.9 (8H, m, 16-H_2, 5, 6, 7, 13-H CH_2), 4.75 (2H, s, CH_2), 5.42-5.52 (2H, m, 10, 11-H), 6.95-7.05 (2H, m, Ar-H_2), 7.69 (1H, d, *J* 8.4Hz, Ar-H); *m/z* (NH_3 DCI)(MH^+), 475.

f) **E-2-{2[5(5S-Hydroxy-4R-methylhex-2E-enyl)-3R,4R-dihydroxy-tetrahydropyran-2S-yl]-1-methylethylidene}5-[1-(1,2-dithiolo[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylmethoxy]indan-1-one** - To the acid from Example 29e (210mg, 0.45mmol) in dry THF (12ml), triethylamine (0.07ml, 0.45mmol) followed by isobutylchloroformate (0.058ml, 0.45mmol) was added, maintaining the external temperature below -10°C. After ½hour, triethylamine (0.09ml, 0.67mmol), followed by 6-amino-1,2-dithiolo[4,3-b]pyrrol-5(4H)one hydrochloride (0.11g, 0.54mmol) were added. After 3½ hours, the reaction was diluted with ethyl acetate and dichloromethane/methanol, silica was added and the mixture evaporated to dryness. The crude product was purified by flash chromatography on silica gel, eluting with 3% methanol in dichloromethane to give a yellow solid. The solid was triturated in dichloromethane, filtered to remove triethylamine hydrochloride, and evaporated to give the title compound as a yellow solid (80mg, 30%); ν_{max} (KBr) 3412, 1667, 1598cm^{-1}; λ_{max} (EtOH) 388.0nm (ε_m 11,079), 297.5nm (ε_m 24,499); δ_H [$(CD_3)_2SO$]; 0.9 (6H, m, 17-H_3, 14-H_3), 1.6 (1H, m, 8H), 2.05 (3H, m, 12-H, 9-H_2), 2.31 (4H, m, 15-H_3, 4-H), 2.65 (1H, d, *J* 12.3Hz, 4-H), 2.8-3.7 (8H, m, CH_2, 6-H_2, 5, 7, 13, 16-H), 4.31 (1H, d, *J* 4.6Hz, OH), 4.69 (2H, m, 2 x OH), 4.88 (2H, s, CH_2),

5.4 (2H, m, 10, 11-H), 6.98-7.05 (2H, m, Ar-H_2), 7.1 (1H, s, C*H*), 7.6 (1H, d, *J* 8.5Hz, Ar-H), 10.1 (1H, s, N*H*), 10.85 (1H, s, N*H*); *m/z* (Electrospray)[*M*-H], 627.

Example 30 - E-2-{2(3R,4R-Dihydroxy-5S[2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydro-pyran-2S-yl]-1-methylidene}5-[3-(1,2-dithiolo[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylpropyloxy]indan-1-one - To the acid from Example 26b (187mg, 0.36mmol) in dry THF (10ml), triethylamine (0.05ml, 0.36mmol) followed by isobutylchloroformate (0.064ml, 0.36mmol) were added at -20°C. After ½hour, a further portion of triethylamine (0.1ml, 0.72mmol) followed by 6-amino-1,2-dithiolo[4,3-b]pyrrol-5(4H)one hydrochloride (85mg, 0.37mmol) were added. The reaction was allowed to warm to room temperature. After 24 hours, dichloromethane was added and the products were washed with water and brine. They were dried over anhydrous magnesium sulphate, filtered and evaporated. Purification by flash chromatography on silica gel eluting with 3% methanol in dichloromethane to 10% methanol in dichloromethane gave title compound as a yellow solid (60mg, 25%); ν_{max} (KBr) 3415, 1672.,1647, 1597cm^{-1}; λ_{max} (EtOH) 391.0nm (ε_m 8,097), 307.5nm (ε_m 17,790); δ_H [$(CD_3)_2SO$]; 0.81 (3H, d, *J* 7.0Hz, 17-H_3), 1.03 (3H, d, *J* 6.4Hz, 14-H_3), 1.31 (1H, m, 12-H), 1.5-1.7 (2H, m, 9-H_2), 1.79 (1H, m, 8-H), 2.0 (2H, t, *J* 6.6Hz, CH_2), 2.32 (4H, m, 15H_3, 4-H), 2.5-2.8 (5H m, CH_2, 10, 11, 4-H), 3.4 (2H, m, 6, 16-H), 3.6-3.7 (6H m, CH_2), 5, 7, 13, 6-H), 4.1 (2H, t, *J* 6.2Hz, CH_2), 4.49 (1H, d, *J* 4.6Hz, O*H*), 4.61 (1H, d, *J* 7.5Hz, OH), 4.7 (1H, d, *J* 3.4Hz, OH), 6.90-7.10 (3H, m, C*H* and Ar-H_2), 7.55 (1H, d, *J* 8.5Hz, Ar-H), 9.9 (1H, s, NH), 10.65 (1H, s, NH); *m/z* (NH_3 DCI)(*M*H$^+$), 673.

Example 31 - 5-[6-(1,2-Dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylhexyl]-2-(1-normon-2-yl)-1,3,4-oxadiazole A

a) N'-(6-carbomethoxyhexoyl)monohydrazide - A solution of suberic acid monomethyl ester (3.73mls) in THF (60ml) at 0°C under argon, was sequentially treated with triethylamine (2.90ml) and isobutyl chloroformate (2.7ml). After 45 minutes the above solution was added to a solution of monohydrazide (6.75g) and pyridine (3.03ml) in acetonitrile (100ml) at 0°C under argon. After a further 45 minutes the reaction was quenched with aqueous sodium hydrogen carbonate and the mixture evaporated to low volume. The residue was extracted with ethyl acetate and the organic phase dried and evaporated. Chromatography on silica eluting with dichloromethane/methanol mixtures gave the title compound (4.02g, 40%); δ_H (CD_3OD) (*inter alia*), 0.95 (3H, d, *J* 7.1Hz, 17-H_3), 1.21 (3H, d, *J* 6.4Hz, 14-H_3), 1.31-1.49 (5H, m, 12-H, 3'-H_2, 4'-H_2), 1.91-2.01 (1H, m, 8-H), 2.19 (3H, s, 15-H_3), 2.20 (3H, m, 4-H, 6'-H_2), 2.61 (1H, d, *J* 14.2Hz, 4-H), 3.58 (1H, d, J 14.2Hz, 16-H),

3.67 (3H, s, OCH_3), and 5.80 (1H, s, 2-H);

b) 5-(6-Carbomethoxyhex-1-yl)-2-(6,7,13-0-tris(trimethylsilyl)-1-normon-2-yl]-1,3,4-oxadiazole A - The product from Example 31a (2.112g, 4mmol) in THF (10ml) was treated with triethylamine (2.8ml, 20mmol), chlorotrimethylsilane (2.54ml, 20mmol) and a catalytic amount of DMAP. After 2 hours at ambient temperature the mixture was filtered and evaporated. The residue was extracted with diethyl ether, and the extract filtered and evaporated to dryness. The resulting residue was dissolved in a mixture of acetonitrile (20ml) and pyridine (20ml) then sequentially treated with triethylamine (1.68ml, 12mmol), carbontetrachloride (2.4ml, 2.4mmol), and tripheylphosphine (3.12g, 12mmol). After 1.5 hours more triethylamine (1.68ml) and triphenylphosphine (3.12g) were added. After a further 1.5 hours the mixture was poured into saturated sodium bicarbonate and extracted with ethyl acetate. The extracts washed with brine then evaporated to dryness. The residue treated with toluene and re-evaporated. Chromatography on silica eluting with ethyl acetate/hexane mixtures gave material containing the title compound (1.53g); δ_H (CD_3OD) (*inter alia*) 2.20 (3H, s, 15-H_3), 2.65 (1H, d, *J* 14.2Hz, 4-H), 3.50-3.60 (2H, m, 16-H, 6-H) 3.65 (3H, s, OCH_3), 3.81-3.96 (4H, m, 13-H, 16-H, 5-H and 7-H), and 6.21 (1H, s, 2-H);

c) 5-(6-Carbomethoxyhex-1-yl)-2-(1-normon-2-yl)-1,3,4-oxadiazole A - The product from Example 31b (1.5g) in THF (40ml) was treated with 0.4M HCl (10ml). After 2 minutes saturated sodium bicarbonate (20ml) was added and the mixture extracted with ethyl acetate. The organic phase was dried and evaporated. Chromatography on silica eluting with dichloromethane/methanol mixtures gave the title compound (1.02g, 100%); ν_{max} (KBr) 1734, 1656, 1576, 1253, 1107, and 1052cm^{-1}; λ_{max} (EtOH) 246nm (εm 18,587); δ_H (CD_3OD) (*inter alia*) 0.93 (3H, d, *J* 7.1Hz, 17-H_3), 1.20 (3H, d, *J* 6.4Hz, 14-H_3), 1.32-1.46 (5H, m, 3'-H_2, 4'-H_2 and 12-H), 1.94 (1H, m, 8-H), 2.25 (3H, s, 15-H_3), 3.40 (1H, dd, *J* 3.1, 9.0Hz, 6-H), 3.58 (1H, d, *J* 11.4Hz, 16-H), and 6.25 (1H, s, 2-H); m/z 510 (M^+, 2%), 266 (100), and 73 (100).

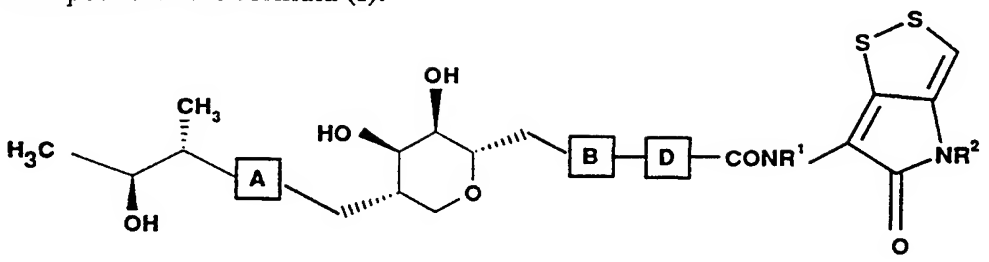
d) 5-(6-Carboxyhex-1-yl)-2-(1-normon-2-yl)-1,3,4-oxadiazole A - Using the method described in Example 8b, the product from Example 31e (500mg) was converted to the title compound (436mg, 90%); δ_H (CD_3OD) (*inter alia*) 0.96 (3H, d, *J* 7.0Hz, 17-H_3), 1.36-1.51 (5H, m, 12H, 3'-H_2 and 4'-H_2), 2.25 (3H, s, 15-H_3), 3.42 (1H, dd, *J* 3.0, 9.0Hz, 6-H), 3.61 (1H, d, *J* 11.3Hz, 16-H), and 6.22 (1H, s, 2-H); m/z 496 (M^+, 18%), 178 (100), and 73 (50).

e) 5-[6-(1,2-Dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylhexyl]-2-[1-normon-2-yl]-1,3,4-oxadiazole A - Using the method described in Example 10, the product of Example 31d (294mg) was converted to the title compound (242mg,

62%); u_{max} (KBr) 3403, 3246, 2924, 2855, 1650, 1539, and 1051 cm^{-1}; l_{max} (EtOH) 387 (e_m 10,800), 303 (3,275), and 245nm(23,891);δ_H (CD_3OD) (*inter alia*) 0.95 (3H, d, *J* 7.3Hz, 17-H_3), 1.20 (3H, d, *J* 6.4Hz, 14-H_3), 1.35-1.50 (5H, m, 12-H, 3'-H_2 and 4'-H_2), 2.21 (3H, s, 15-H_3), 3.39 (1H, dd, *J* 3.1, 9.0Hz, 6-H), 3.58 (1H, d, *J* 10.9Hz, 16-H), 6.21 (1H, s, 2-H), and 7.07 (1H, s, 3"-H); d_C (CD_3OD) 12.23 (C-17), 20.07, 20.30 (C-14, 15), 25.76, 26.40, 27.16, 29.56, 29.58, 36.41 (C-1", 2", 3", 4", 5", 6"), 32.98 (C-9), 41.70 (C-8), 43.71 (C-12), 43.78 (C-4), 56.68 (C-10), 61.26 (C-11), 66.37 (C-16), 69.98 (C-6), 70.30 (C-13), 70.70 (C-7), 76.52 (C-5), 109.76 (C-2), 113.52, 120.36, 135.07, 137.89, 170.36 (C-3"', 3a"', 5"', 6"', and 6a"'), 153.01 (C-3), 165.51 (C-5'), 167.45 (C-1), and 174.15 (C-7").

Claims

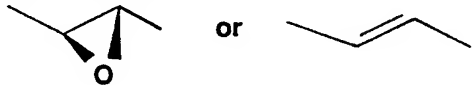
1. A compound of the formula (I):



(I)

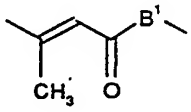
in which:

A is an epoxy moiety or an E-double bond moiety:



B is selected from the following:

(a)



in which:

B^1 is a group X^1, X^2, Y^1, NH or NHX^1,

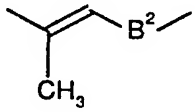
in which:

X^1 is optionally substitued aryl;

X^2 is (C_{1-10})alkylene, (C_{2-10})alkenylene, (C_{2-10})alkynylene, (C_{3-7})cycloalkylene or aryl(C_{1-4})alkylene, each of which may be optionally substituted; and

Y^1 is optionally substituted heterocyclyl;

(b)



in which:

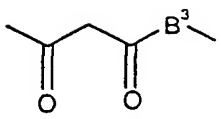
B^2 is Y^2, Y^2-X^1, Y^2-X^2 or Y^2-Y^3 in which:

Y^2 is a 5- or 6- membered heteroaryl ring having from 1 to 4 heteroatoms, each selected from oxygen, sulphur or nitrogen and optionally substituted by (C_{1-10})alkyl, (C_{2-10})alkenyl, (C_{2-10})alkynyl, (C_{3-7})cycloalkyl, aryl(C_{1-4})alkyl, aryl or heterocyclyl;

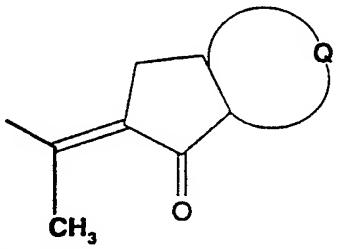
Y^3 is an optionally substituted heterocyclic ring; and

X^1 and X^2 are as hereinbefore defined;

(c)



(which corresponds to C(OH)=CHCO-B^3),
in which B^3 is an optionally substituted hydrocarbyl or heterocyclyl group; or
(d)



in which Q denotes the residue of an optionally substituted aryl or heteroaryl ring;
D is a group of atoms for linking B with -CONR^1; or
B-D represents (E)-C(CH_3)=CH; and
R^1 and R^2, which may be the same or different, is each selected from hydrogen or (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{2-6})alkenyl, aryl, aryl(C_{1-4})alkyl, heterocyclyl, (C_{1-6})alkylcarbonyl, (C_{3-7})cycloalkylcarbonyl, (C_{2-6})alkenylcarbonyl, arylcarbonyl, aryl(C_{1-4})alkylcarbonyl or heterocyclylcarbonyl, each of which may be optionally substituted.

2. A compound of formula (I) as claimed in claim 1 in which the linking group of atoms D comprises one or more carbon atoms which may include carbon atoms in a carbocyclic ring and/or heteroatoms which could include heteroatoms in a heterocyclic ring.

3. A compound of formula (I) as claimed in claim 1 or 2 in which D is a hydrocarbylene chain containing up to 20 carbon atoms which chain may be:
(a) optionally substituted,
(b) optionally interrupted at one or more places by a moiety M,
(c) joined to B^1, B^2, B^3 or Q by a suitable linkage, and
(d) joined to -CONR^1 by a suitable linkage; and
in which M represents a heteroatom selected from oxygen, sulphur or nitrogen; a (C_{3-7})cycloalkylene group; a carbon-carbon double bond; a carbon-carbon triple bond; CO; OC(O); C(O)O; NRCO; C(O)NR; NRCONR; NRC(O)O; OC(O)NR: SO_2NR; NRSO_2; CONRSO_2; SO_2NRCO and phenyloxy; in which R is hydrogen or (C_{1-6})alkyl.

4. A compound of formula (I) as claimed in claim 3 in which in (c), the linkage is a

direct bond, a heteroatom selected from oxygen, sulphur or nitrogen, carbonyloxy (COO), oxycarbonyl (OCO), carbonate(OCOO), carbamoyl (CONH), NHCO, NHCONH, SO_2, and SO_2NH.

5. A compound of formula (I) as claimed in claim 3 in which in (d), the linkage is a direct bond, optionally substituted (C_{3-7})cycloalkylene, optionally substitued aryl or optionally substituted heterocyclyl.

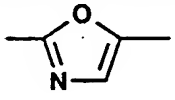
6. A compound of formula (I) as claimed in claim 3 in which the hydrocarbylene chain is a polymethylene chain having between between 1 and 20 carbon atoms.

7. A compound of formula (I) as claimed in claim 6 in which polymethylene chain has between 1 and 12 carbon atoms.

8. A compound of formula (I) as claimed in any one of claims 1 to 7 in which D is an oxyalkylene chain $O(CH_2)_n$ or an alkylene chain $(CH_2)_n$ in which n is an integer between 1 and 12.

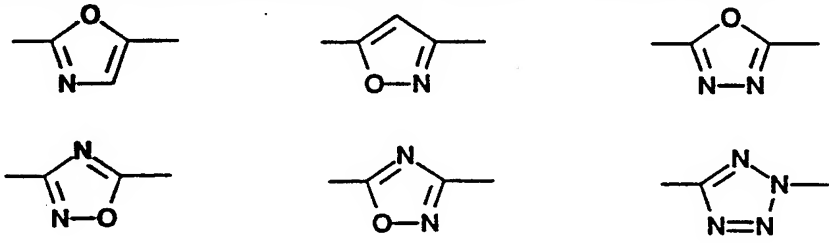
9. A compound of formula (I) as claimed in any one of claims 1 to 8 in which Y^1 is selected from furan, thiophene, pyrrole, benzofuran, benzothiophene, indole, oxazole, isoxazole, thiazole, isothiazole, pyrazole, benzimidazole, oxadiazole, thiadiazole, triazole, tetrazole, thiatriazole, pyridine, quinoline, isoquinoline, pyrazine, pyrimidine, pyridazine and triazine.

10. A compound of formula (I) as claimed in claim 9 in which Y^1 is:

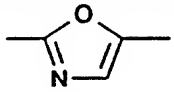


11. A compound of formula (I) as claimed in any one of claims 1 to 10 in which Y^2 is furan, thiophene, pyrrole, diazole, oxazole, thiazole, isoxazole, isothiazole, triazole, oxadiazole, thiadiazole or tetrazole.

12. A compound of formula (I) as claimed in claim 11 in which Y^2 is:



13. A compound of formula (I) as claimed in claim 12 in which Y^2 is:

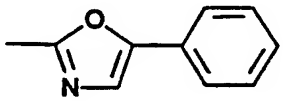


14. A compound of formula (I) as claimed in any one of claims 1 to 13 in which Y^3 is:

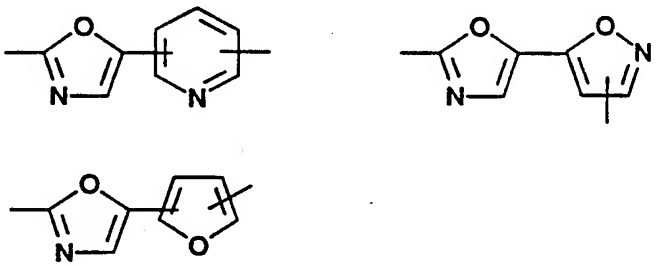
15. A compound of formula (I) as claimed in any one of claims 1 to 14 in which B^3 is a group B^4-B^5 in which B^4 is (C_{1-6})alkylene, (C_{2-6})alkenylene, (C_{2-6})alkynylene and B^5 is a direct bond, (C_{3-7})cycloalkylene, (C_{4-7})cycloalkenylene, aryl or heteroaryl, each of which may be optionally substituted; or B^4 is a bond and B^5 is (C_{3-7})cycloalkyene, (C_{4-7})cycloalkenylene, aryl or heteroaryl.

16. A compound of formula (I) as claimed in claim 15 in which B^4 is a direct bond and B^5 is pyrimidine, thiazole, oxazole, pyridine or phenyl.

17. A compound of formula (I) as claimed in any one of claims 1 to 16 in which Y^2-X^1 is:



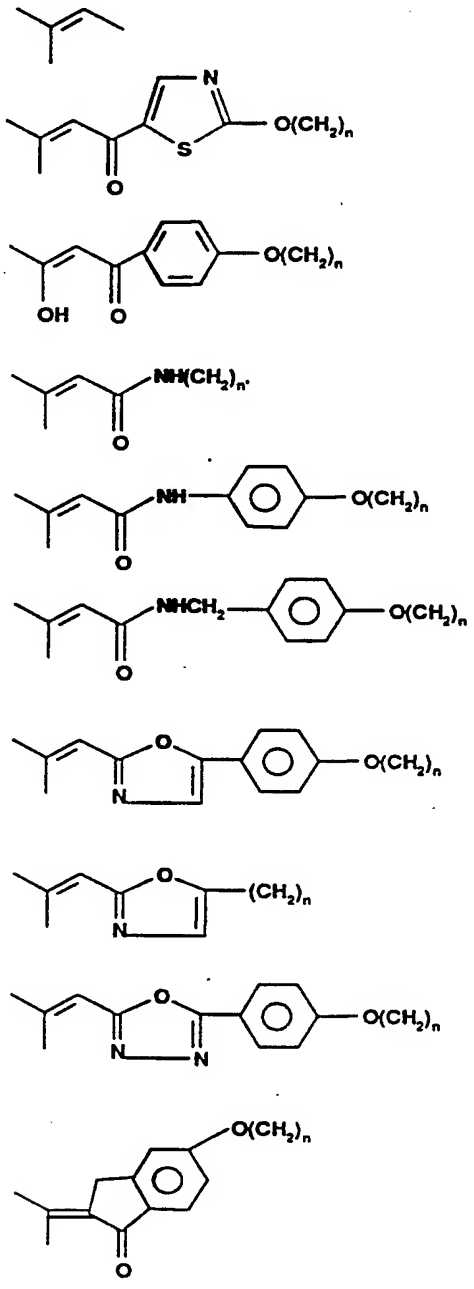
18. A compound of formula (I) as claimed in any one of claims 1 to 17 in which Y^2-Y^3 is:



19. A compound of formula (I) as claimed in any one of claims 1 to 18 in which Q forms the residue of a benzene ring which may be unsubstituted or substituted by up to three further substituents, in addition to D.

20. A compound of formula (I) as claimed in any one of claims 1 to 18 in which Q forms the residue of a pyridine or furan ring, which ring may be unsubstituted or substituted by up to two further substituents, in addition to D.

21. A compound of formula (I) as claimed in any one of claims 1 to 20 in which B-D is:



n = 1 to 6;
n'= 6 to 12

22. A compound of formula (I) as claimed in any one of claims 1 to 21 in which R^1 is hydrogen.

23. A compound of formula (I) as claimed in any one of claims 1 to 22 in which R^2 is hydrogen.

24. A compound of formula (I) as defined in claim 1, selected from the following:
3R,4R-Dihydroxy-2S-[2,4-dioxo-4-{4-(4-methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylbut-1-yloxyphenyl}but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
N-(4-Methyl-1,2-dithiolo-[4,3-b]-5-(4H)-oxopyrrolo-6-yl)-monamide A;
2-{6-(4-Methyl-1,2-dithiolo-[4,3-b]-5-(4H)-oxopyrrol-6-yl)]carbamoylhexoxy}-thiazol-5-yl-1-normon-2-yl ketoneExample 3 - 2-{6-(4-Methyl-1,2-dithiolo-[4,3-b]-5-(4H)-oxopyrrol-6-yl)]carbamoylhexoxy}-thiazol-5-yl-1-normon-2-yl ketone - A series;
2-{6-(4-Methyl-1,2-dithiolo-[4,3-b]-5-(4H)-oxopyrrol-6-yl)carbamoylhexoxy}-thiazol-5-yl-1-normon-2-yl ketone - C series;
N-{8-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]octan-1-yl}monamide A;
N-{8-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]octan-1-yl}monamide C;
5-(4-(3-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylprop-1-oxy)phenyl)-2-(1-normon-2-yl)oxazole A;
5-[4-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylmethyloxy-phenyl]-2-(1-normon-2-yl)oxazole A;
3R,4R-Dihydroxy-2-S-[2,4-dioxo-4-{4-[3-(4-methyl-1,2-thiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbomoylprop-1-yloxy]phenyl}but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
3R,4R-Dihydroxy-2S-[2,4-dioxo-4-{4-[4-(1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylbut-1-yloxy)phenyl}but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
3R,4R-Dihydroxy-2S-[2,4-dioxo-4-{4-(3-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylprop-1-yloxy]phenyl}but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
2-{4-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylbutoxy}thiazol-5-yl 1-normon-2-yl ketone A;
2-{1,2-Dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl}carbamoylmethyloxythiazol-5-yl 1-normon-2-yl ketone A;

N-{8-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]-2-oxooct-1-yl}monamide A;

5-[6-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylhexyl]-2-(1-normon-2-yl)oxazole A;

5-[6-(1,2-Dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylhexyl]-2-(1-normon-2-yl)oxazole A;

5-[4-(1,2-Dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylmethyloxyphenyl]-2-(1-normon-2-yl)oxazole A;

N-{4-[3-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-ylaminocarbonyl)-propyloxy]phenyl}monamide A;

N-{4-[4-(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-ylaminocarbonyl)-butyloxy]benzyl}monamide A;

N-{8-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]-octyl}monamide A;

N-{9-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]-nonyl}monamide A;

N-{10-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]-decyl}monamide A;

N-{11-[(4-Methyl-1,2-dithiolo-[4,3-b]-5(4H)-oxopyrrol-5-yl)carbamoyl]-undecyl}monamide A;

N-{9-[(1,2-Dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl]nonyl}monamide A;

E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran-2S-yl]-1-methylethylidene}-5[5-(4-methyl-1,2-dithiolo[4,3-b]-5-(4H)-oxopyrrol-6-yl)carbamoylpent-1-yloxy]indan-1-one;

E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran-2S-yl]-1-methylethylidene}-5-[3-(4-methyl-1,2-dithiolo[4,3-b]-5-(4H)-oxopyrrol-6-yl)carbamoylprop-1-yl]indan-1-one;

E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl) tetrahydropyran-2S-yl]-1-methylethylidene}-5-[1-(4-methyl-1,2-dithiolo[4,3-b]-5-(4H)-oxopyrrol-6-yl)carbamoylmethoxy]indan-1-one;

E-2-{2-[3R,4R-Dihydroxy-5S(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran-2S-yl]-1-methylethylidene}5-[1-(1,2-dithiolo[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylmethoxy]indan-1-one;

E-2-{2[5(5S-Hydroxy-4R-methylhex-2-enyl)-3R,4R-dihydroxytetrahydropyran-2S-yl]-1-methylethylidene}5-[1-(1,2-dithiolo[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoyl-methoxy]indan-1-one;

E-2-{2(3R,4R-Dihydroxy-5S[2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydro-pyran-2S-yl]-1-methylidene}5-[3-(1,2-dithiolo[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylpropyloxy]indan-1-one; and

5-[6-(1,2-Dithiolo-[4,3-b]-5(4H)-oxopyrrol-6-yl)carbamoylhexyl]-2-(1-normon-2-yl)-1,3,4-oxadiazole A.

25. A pharmaceutical or veterinary composition which comprises a compound of formula (I) as defined in any one of claims 1 to 24 together with a pharmaceutically or veterinarily acceptable carrier or excipient.

26. A compound of formula (I) as defined in any one of claims 1 to 24 for use in therapy.

27. The use of a compound of formula (I) as defined in claim 1 in the manufacture of a medicament for treating bacterial infections in human and non-human animals.

28. The use of a compound of formula (I) as defined in claim 1 in the manufacture of a medicament for treating mycoplasmal infections in human and non-human animals.

29. The use of a compound of formula (I) as defined in claim 1 in the manufacture of a medicament for treating fungal infections in human and non-human animals.

30. A method of treating bacterial infection in human and non-human animals which method comprises administering an anti-bacterially effective amount of a compound of formula (I) as defined in claim 1 to a patient in need thereof.

31. A method of treating mycoplasmal infection in human and non-human animals which method comprises administering an anti-mycoplasmal effective amount of a compound of formula (I) as defined in claim 1 to a patient in need thereof.

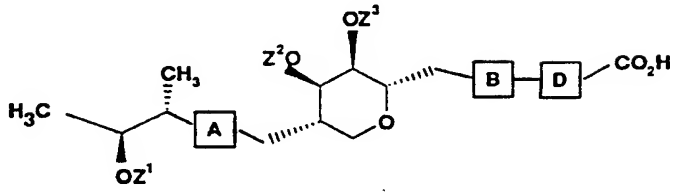
32. A method of treating fungal infection in human and non-human animals which method comprises administering an anti-fungal effective amount of a compound of formula (I) as defined in claim 1 to a patient in need thereof.

33. A process of severely damaging or killing unwanted plants which process comprises applying to the plants or the growth medium of the plants a herbicidally effective amount of a compound of formula (I) as defined in claim 1.

34. A herbicidal composition which comprises a compound of formula (I) as defined in any one of claims 1 to 24 together with a herbicidally accepatable carrier.

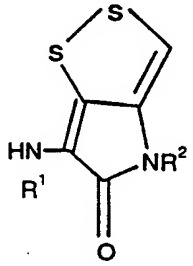
35. A process for preparing a compound of formula (I) as defined in claim 1 which

process comprises reacting an acid of formula (IV):



(IV)

in which Z^1, Z^2 and Z^3, which may be the same or different, is each hydrogen or a hydroxyl protecting group, and A, B and D are as defined in claim 1;
or an activated derivative thereof;
with an amine of formula (V):



(V)

in which R^1 and R^2 are as defined in claim 1;
under amide forming conditions;
and thereafter removing any hydroxyl protecting groups.

36. A process as claimed in claim 35 in which the amide forming conditions comprise reacting an acyl halide or a mixed anhydride derivative of an acid of formula (IV) with an amine of the formula (V) in the presence of a suitable base in an aprotic solvent and at a moderate temperature.

37. A compound of formula (IV) as defined in claim 33, excluding:
E-2-{2-[3R,4R-*Bis*-trimethylsilyloxy-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran-3S-yl]-(1-methylethylidene)}-5-t-butyldimethylsilyloxyindan-1-one;
E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran-2S-yl]-(1-methylethylidene)}-5-hydroxyindan-1-one;
E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran-2S-yl]-1-methylethylidene}-5-(methoxycarbonylpent-1-yloxy)indan-1-one; and
E-2-{2-[3R,4R-Dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl) tetrahydropyran-2S-yl]-1-methylethylidene}-5-(5-carboxypent-1-yloxy)indan-1-one.

38. A compound as claimed in claim 1 substantially as hereinbefore defined with reference to any one of the Examples.

39. A process as claimed in claim 36 substantially as hereinbefore defined with reference to any one of the Examples.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 94/02552

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D495/04 A61K31/40 A01N43/90 C07D407/06 C07D417/14 C07D417/06 C07D413/14 C07D309/10 //(C07D495/04,339:00, 209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 001 914 (BEECHAM GROUP LIMITED) 16 May 1979 cited in the application see page 22 - page 23; claims 1,6-8 see page 2, line 21 - page 3, line 6	1,21-28, 35
X	see page 9 - page 16; examples 3,5,7,9,10 cited in the application ---	37
X	EP,A,0 087 953 (BEECHAM GROUP PLC) 7 September 1983 cited in the application see page 37 - page 39; example 7 see page 47; example 12 see page 53 - page 54; examples 16,17	37
A	see page 1; claim 1 cited in the application see page 18, paragraph 4 --- -/--	1-28

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 December 1994	14. 12. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Fink, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 94/02552

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 15072 (SMITHKLINE BEECHAM PLC) 5 August 1993 see page 19; examples 5,6	37
A	see page 21; claims 1,6,7	1-28
X	JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, 1982, LETCHWORTH GB pages 2827 - 2833 J.P. CLAYTON ET AL. cited in the application see page 2828; column 1, compounds no. 1(d)-1(f), 1(h) and 2(d)-2(f)	37
X	JOURNAL OF MEDICINAL CHEMISTRY, vol.32, no.1, 1989, WASHINGTON US pages 151 - 160 L.L. KLEIN ET AL. cited in the application see page 155; table I, entries no. 1, 2, 8 and 17	37
A	EP,A,0 512 824 (SANKYO COMPANY LIMITED) 11 November 1992 cited in the application see page 2, line 38 - line 50 see page 3, line 2 - line 3	1-28

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 94/02552

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 30-32 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/compositon.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 94/02552

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0001914	16-05-79	AU-B-	526219	23-12-82
		AU-A-	4135078	17-05-79
		JP-A-	54084577	05-07-79
		US-A-	4200635	29-04-80
EP-A-0087953	07-09-83	AU-B-	563067	25-06-87
		AU-A-	1185383	01-09-83
		CA-A-	1195983	29-10-85
		DE-A-	3376424	01-06-88
		JP-B-	6004627	19-01-94
		JP-A-	58159491	21-09-83
		US-A-	5041567	20-08-91
		US-A-	4812470	14-03-89
WO-A-9315072	05-08-93	AU-B-	3361393	01-09-93
		CN-A-	1088926	06-07-94
		EP-A-	0623130	09-11-94
EP-A-0512824	11-11-92	AU-B-	646615	24-02-94
		AU-A-	1603392	12-11-92
		CN-A-	1067921	13-01-93
		JP-A-	5132486	28-05-93
		NZ-A-	242648	25-03-94
		US-A-	5292892	08-03-94